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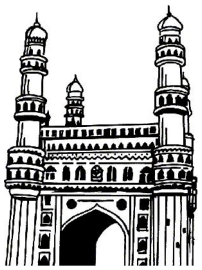

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UNIT - I

(Medicinal Chemistry)

Introduction and Terminology

S6-E-A-I: Diseases: Common diseases, infective diseases-insect borne, air-borne, water-borne and hereditary diseases. Terminology in Medicinal Chemistry: Drug, Active Pharmaceutical Ingredient (API), Pharmaceuticals, Pharmacology, Pharmacophore, Pharmacodynamics, Pharmacokinetics, metabolites, anti metabolites and therapeutic index.

Drugs: Nomenclature: Chemical name, Generic name and Trade names with examples;

Classification: Classification based on structures and therapeutic activity with examples.

ADMET: a) Absorption: Definition, absorption of drugs across the membrane - active and passive absorption, routes of administration of drugs, b) Distribution: definition and effect of plasma protein binding, c) Metabolism: definition, phase I and phase II reactions, d) Elimination: definition and renal elimination. Toxicity.

S6-E-A-I: Diseases

Q1. What is Diseases ?

Ans :

Disease can be defined as an endogenous biochemical imbalance, an abnormal and aberrant proliferation of cells, or an exogenous chemical toxin or an invasive pathogen in the body.

Q2. Mention the types of disease.

Ans : **(Imp.)**

The pathogens may enter the air in wet droplets, for example, when someone breathes or sneezes. There, they will be suspended in the air, and some droplets dry out, leaving microscopic particles. While suspended in the air, these particles can attach to or enter the body systems of people nearby. Many diseases can arise after exposure to airborne particles, including:

- The common cold, which can develop from a rhinovirus
- Chickenpox, caused by the Varicella zoster virus
- Mumps, caused by a paramyxovirus
- Measles, caused by another paramyxovirus
- Whooping cough, a bacterial infection caused by Bordetella pertussis
- COVID-19, caused by the SARS-CoV-2 virus
- Aspergillosis, caused by the Aspergillus fungus
- Tuberculosis (TB), caused by the bacterium Mycobacterium tuberculosis
- Anthrax, a bacterial infection resulting from contact with Bacillus anthracis spores
- Diphtheria, a bacterial infection caused by Corynebacterium diphtheriae
- Meningitis, which can result from exposure to certain bacterial, viral, or fungal particles

Some experts believe influenza transmits through the air.

Airborne diseases are spread when droplets of pathogens are expelled into the air due to coughing, sneezing or talking. Water-borne disease is any disease that is caused by pathogenic microorganisms and most commonly transmitted through contact or consumption of infected water.

Common Infectious Diseases

1. Chickenpox.
2. Common cold.
3. Diphtheria.
4. E. coli.
5. Giardiasis.
6. HIV/AIDS.
7. Infectious mononucleosis.
8. Influenza (flu)

1. Common diseases in human beings

i) Disease can be defined as a disorder or malfunction of the mind or body. It involves morphological, physiological and psychological disturbances which may be due to environmental factors or pathogens or genetic anomalies or life style changes. Diseases can be broadly grouped into infectious and non infectious types.

ii) Diseases which are transmitted from one person to another are called infectious diseases or communicable diseases. Such disease causing organisms are called pathogens and are transmitted through air, water, food, physical contact and vectors. The disease causing pathogen may be virus, bacteria, fungi, protozoan parasites, helminthic parasites, etc., Infectious diseases are common and everyone suffers from such diseases at some time or the other. Most of the bacterial diseases are curable but all viral diseases are not. Some infectious disease like AIDS may be fatal.

iii) Non-infectious diseases are nottransmitted from an infected person to a healthy person. In origin they may be genetic (cystic fibrosis), nutritional (vitamin deficiency diseases) and degenerative (arthritis, heart attack, stroke). Among non - infectious diseases, cancer is one of the major causes of death.

iv) Airborne diseases are caused by pathogenic microbes small enough to be discharged from an infected person via coughing, sneezing, laughing and close personal contact or aerosolization of the microbe. The discharged microbes remain suspended in the air on dust particles, respiratory and water droplets.Airborne diseases are caused by pathogenic microbes small enough to be discharged from an infected person via coughing, sneezing, laughing and close personal contact or aerosolization of the microbe. The discharged microbes remain suspended in the air on dust particles, respiratory and water droplets.

v) These diseases are caused by consumption of water contaminated by human or animal excreta i.e. diarrhoea, cholera, typhoid and gastro-enteritis etc.

vi) The human and animal excreta contain various disease causing microorganisms such as bacteria, virus, worms and amoeba

2. Typhoid

i) Typhoid fever is caused by Salmonella typhosa bacteria by ingesting contaminated food and water. Symptoms are characterized by headache, nausea, loss of appetite.

ii) It can be prevented by providing access to safe drinking water, sanitation and good hygiene.

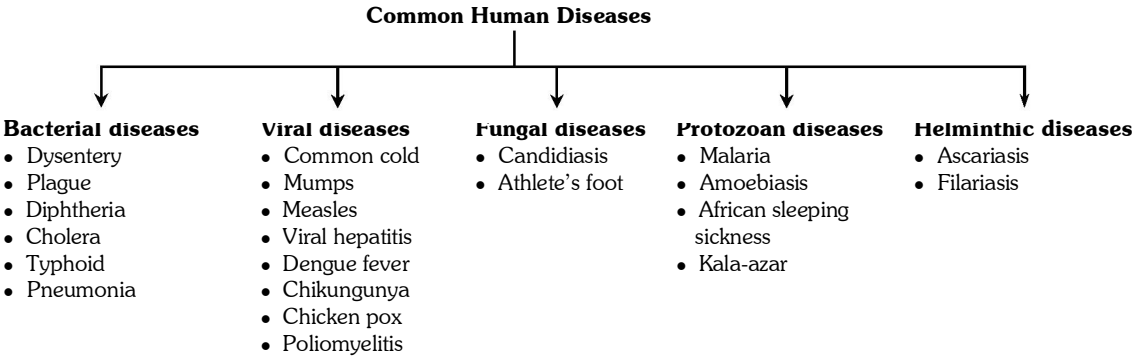
3. Cholera

i) It is highly contagious disease and caused by Vibrio cholerae bacteria.

ii) Typical symptoms include diarrhoea, vomiting, rapid dehydration, muscular cramps etc.

iii) It can be controlled by early detection of the disease, improving sanitation facilities and prompt treatment.

iv) Tetracycline and Cotrimoxozole should be administered as antibiotic S



Q3. Define drug.

Ans :

A drug is defined as an agent intended for use in the diagnosis, mitigation, treatment, cure or prevention of disease in man or in other animals. According to World Health Organisation (WHO), who promote basic health globally, "A drug is any substance or product that is used or intended to be used to modify or explore physiological systems or pathological states for the benefit of the recipient."

Q4. Give the standard name of API and define it.

Ans :

Active pharmaceutical ingredients (APIs)

Active pharmaceutical ingredients (APIs) are the active components in a pharmaceutical drug that produce the required effect on the body to treat a condition. APIs are produced by processing chemical compounds.

API is the biologically active component of a drug product (tablet, capsule, cream, Injectable) that produces the intended effects. The main ingredient in a medicine that causes the desired effect of medicine.

API is a chemical compound that is the most important raw material to produce a finished medicine.

API are Mainly Two Types

1. Signthetic chemical API $\rightarrow$ ex: ASPIRIN
2. Natural chemical API $\rightarrow$ ex : Humira, Femicade

Example

1. Paracetamol is the API for crocin it is the API that gives relief from body ache + fever.
2. Ibuprofin is an API. Which is used to produce Ibuprofin drug. The finished drugs Ibuprofin is most nonsteroidal anti-inflammatory drug.

Q5. Write about pharmaceuticals.

Ans :

The pharmaceutical industry discovers, develops, produces, and markets drugs or pharmaceutical drugs for use as medications to be administered to patients (or self-administered), with the aim to cure them, vaccinate them, or alleviate symptoms.

Pharmaceutical is substances used in the diagnosis, treatment (or) prevention of diseases for restoring, correcting (or) modifying organic functions.

Pharmaceutical medicine is the medical specialty concerned with the research, development and maintaining monitoring of new medicine. It involves the design, development evaluation of drugs in combination with an appropriate dosage form.

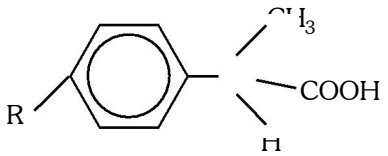
Q6. What is pharmacophore give example.

Ans : **(Imp.)**

Pharmacophore

The parts of the drug molecule that interact with the receptor and are responsible for biological activity are known as the pharmacophore of the compound. Any structural alterations of the pharmacophore from the molecule of a drug either lessens or totally destroys its medicinal value.

The common structural feature in all the three anti-inflammatory drugs is aryl methylacetic acid.



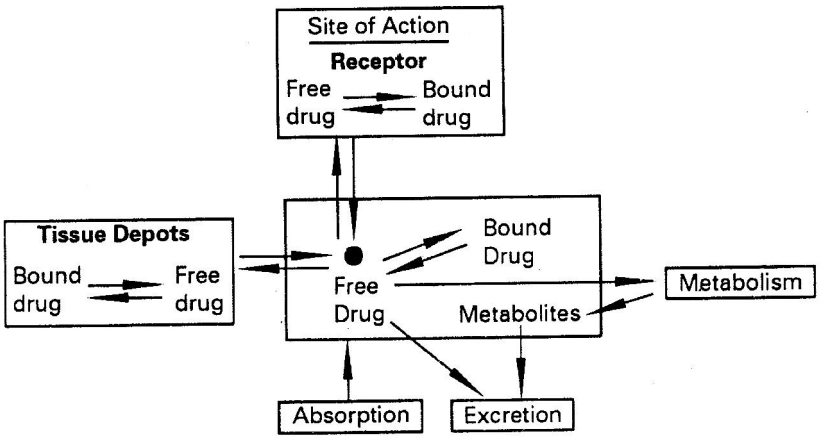
The molecular fragment which binds with the receptor and is responsible for its biological action, is called the pharmacophore of the drug. Therefore, the pharmacophore is related to the pharmacodynamics of the drug. The other part of the drug molecule is commonly called the non -pharmacophore of the drug. The non-pharmacophore mostly decides the pharmacokinetics of the drug. Changes in the molecular structure of the pharmacophore part lead to the loss of a specific drug property, while changes in the non-pharmacophore part may not change the drug properties.

Q7. Explain about pharmacodynamics & pharmacokinetics.

Ans : **(Imp.)**

i) Pharmacokinetics

Pharmacokinetics is the study of Absorption, Distribution, Metabolism (biotransformation), and Excretion (ADME) of drugs. This study give us information about the drug concentration in the blood and tissues at different time intervals (time-course of the drug) and will decide the dosage.



To study the pharmacokinetics of the drug. This deals with : i) how drugs cross membranes (absorbed) to enter the body tissues, ii) how they are distributed in the blood and other body tissues, iii) how they are transformed (metabolized) to other compounds, and iv) how they are eliminated (excreted) from the body. It is necessary for the drugs to pass across cell membranes, which are essentially bilayers of lipid molecules.

ii) Pharmacodynamics

Broadly, the action of any drug involves two stages: (i) the journey of the drug molecule from its point of entry into the body (enterally, parentally, etc.) to the site of action (pharmacokinetics, i.e., ADME) and (ii) the interaction of the drug with the specific biological macromolecule of the human body (such as proteins or DNA), or the biological macromolecules (such as proteins or DNA) of the bacteria, in the case of bacterial infections.

The bilogical macromolecule in the human body or bacteria or virus with which the drugs bind, leading to the drug action, is called a receptor. These receptors are the targets for the drugs. Receptors are drug-reecognition and drug-binding sites in the cells of the human body, tumor cells or bacteria. Receptors are located in different tissues of the body, e.g., CNS, lungs, gastric cells, and so on.

Q8. What are receptors give examples?

Ans :

Receptors

Pharmacodynamics deals with the interaction of the drug with the receptor. This includes: (1) the recognition of the drug molecule by the receptor; (2) the binding of the drug with the receptor; generally by H-bonding or ionic bonding or vander Waals forces involving the functional groups of the drug and the functional groups of the receptor, and (3) translating the drug-receptor binding into a biological response (drug action). This entire series of action put together is known as pharmacodynamics.

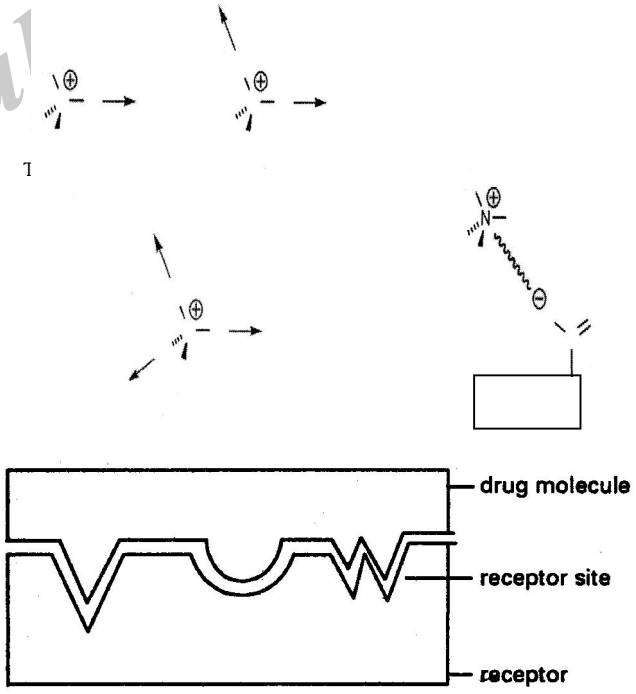


Fig.: Lock and Key Model of the Drug-receptor interaction

The interaction of the drug with the receptor was analogous to a lock and key, i.e., a specific molecular structure of the drug can interact to fit and bind with only one kind of receptor molecule. The chemical functional groups of the receptor bind with the complimentary functional groups of the drug molecule. The figure illustrates the antihypertensive drug, captopril, binding at the ACE receptor. One can observe H-bonding, ionic bonding, and ion-dipole bonding between the drug and the receptor. The site or spaces in the receptor molecule containing the functional groups that aid in binding to the drug is called the receptor site.

The receptors, which are chemically macromolecules, are mainly of two types:

(i) Protein receptors, and

(ii) DNA receptors

The majority of receptors are proteins. A protein is a macromolecule (high molecular weight) and is built up of about 200-300 amino acid units. Proteins control and or catalyze all the cellular reactions and are responsible for all the cell functions. Many drugs are targeted to these protein receptors, to control or alter the cellular functions. DNA controls the replication of the cells. In the case of tumour (cancer), the cell multiplies more rapidly than the normal cells. Drugs can be targeted to the tumour cell DNA, (now called a receptor) which, by binding to it, can prevent the DNA replication and thereby control the tumour cell proliferation.

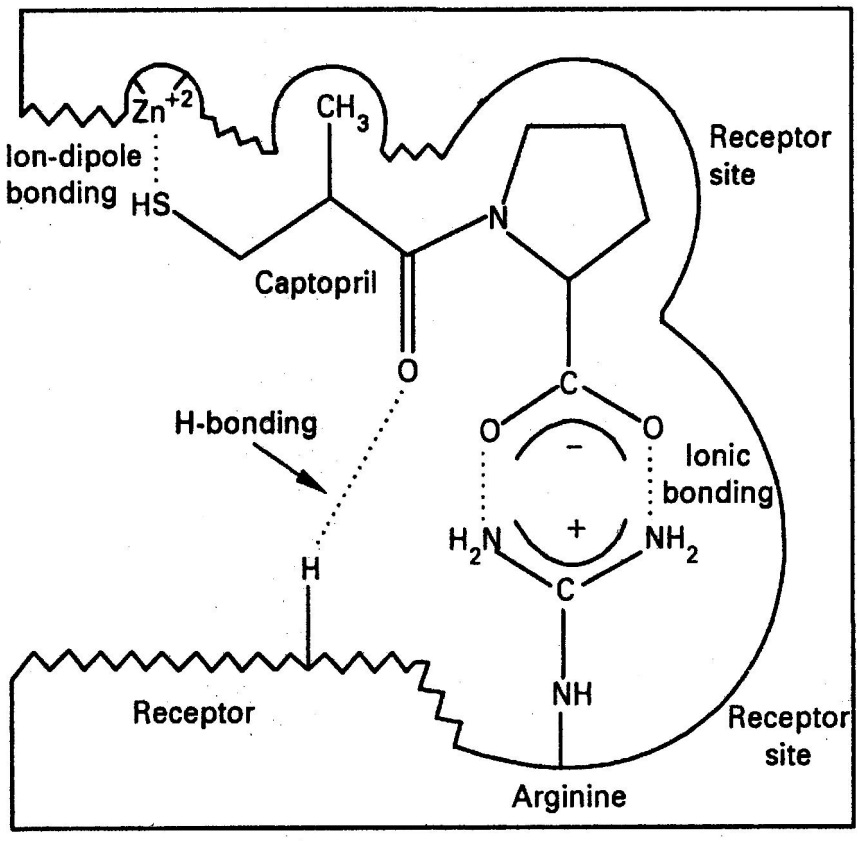


Fig.: Captopril binding at the receptor, the Angiotensin Converting Enzyme (ACE)

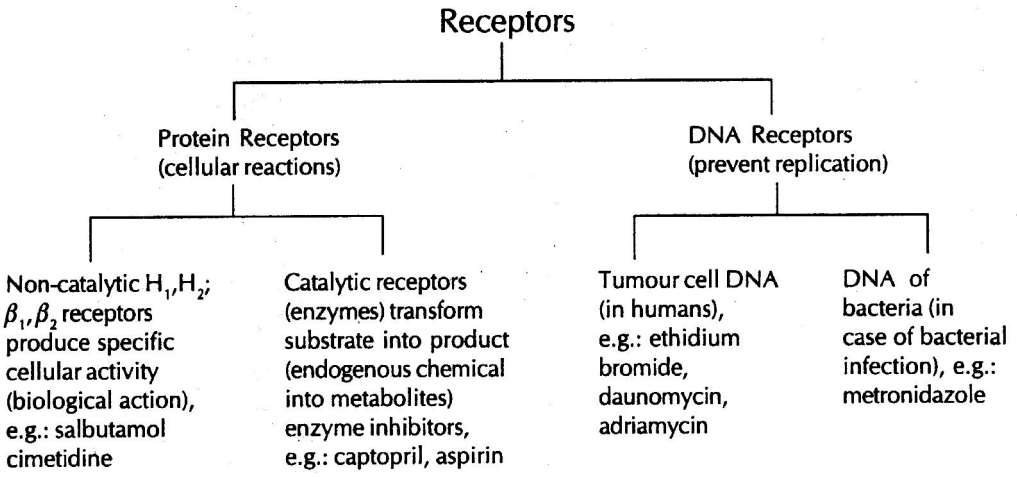


Fig.: Classification of receptors

Protein receptors

In the human body, protein receptors are broadly classified into two classes:

(i) Non-catalytic protein receptors, and

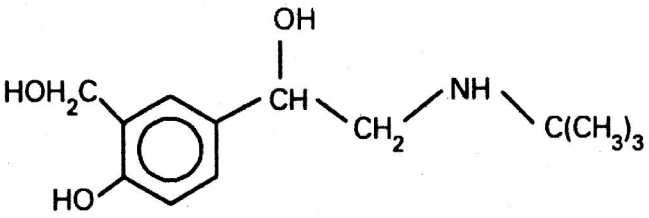
(ii) Catalytic protein receptors

In a normal situation, i.e., in the absence of the drug, the non-catalytic proteins (e.g: H1 receptor, H2 receptor, β-adrenergic receptor, β-adrenergic receptor) bind with an endogenous chemical (a chemical already present in the body), such as histamine and adrenaline, and produce specific cellular activity or functions.

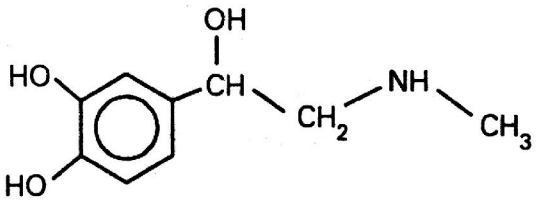
Catalytic proteins are also known as enzymes. An enzyme, on the other hand, transforms an endogenous chemical (substrate) into another chemical (product). Enzymes catalytically produce several metabolites, which are responsible for the cellular functions.

Many diseases are due to the altered biochemistry of the cells, i.e., there is either a deficiency or excess of an endogenous chemical. In such a situation, the normal biological activity due to the non-catalytic or catalytic receptors is altered. A drug (exogenous chemical) is now needed to alter or regulate the specific biochemical reaction by interaction with the non-catalytic or catalytic receptors. The drugs are, therefore, targeted to these non-catalytic or catalytic receptors.

Non-catalytic protein receptors Adrenaline (26), an endogenous chemical, by binding to the β-adrenergic receptor produces bronchodilation. If there is less adrenaline in the body, it leads to symptoms of asthma. When salbutamol (25) is used as the drug, this drug binds with the β-adrenergic receptor to cause bronchodilation similar to that produced by adrenaline; as their chemical structures are similar. Salbutamol increases the overall bronchodilation. The bronchodilation is now due to both endogenous adrenaline and the drug salbutamol. Drugs like salbutamol, which bind with a receptor and produce a biological action similar to that of an endogenous chemical, are called agonist drugs.

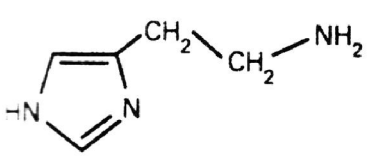


Salbutamol

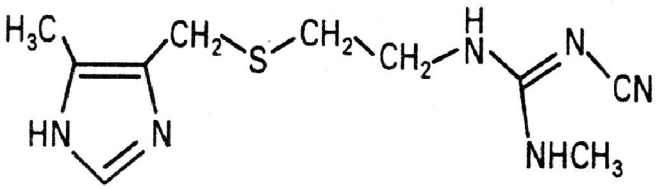


Adrenaline

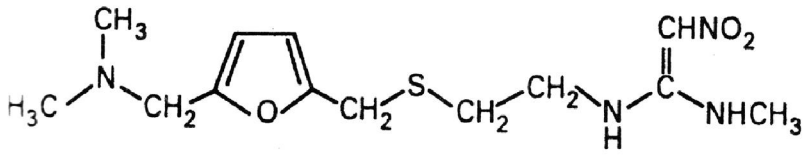
Histamine , on binding to the H2 histamine receptor in the gastric cells, leads to the production of HCI which is necessary for the digestion of food. In people who suffer from tension, worry, etc., there is an excess production of HCI as more histamine is released in the gastric cells. Drugs like cimetidine or ranitidine, whose chemical structure is not very similar to histamine, occupy and bind with the receptor site on H2 receptors and prevent the excessive production of HCI. So, there is now a competition between the histamine and cimetidine for the same H2 receptor. The histamine-bound H2 receptor as usual produces HCI, while the cimitidine-bound H2 receptor cannot produce any HCI. Drugs like cimitidine which can only bind and block a receptor but do not produce any biological action, are known as antagonists or blockers.



Histamine



Cimetidine



Ranitidine

There are two aspects of drug-receptor interactions. They are: (i) the tendency of drug molecule to bind to the surface of the receptor, called the 'affinity' of the drug, and (ii) the ability of the drug-receptor-complex to initiate a biological response, which is called 'efficacy' or 'intrinsic activity'- The pharmacological activity depends on the rate of association and dissociation of the drug with the receptor. In general, while antagonists bind tightly to a receptor (great affinity), and are devoid of biological activity (no efficacy or intrinsic activity)agonists will have both affinity and efficacy . In the case of agonists, the rate of both association and dissociation with the receptor would be quick (the latter quicker than the former). The rate of association of an antagonist with the receptor would be quick, but the dissociation would be slow.

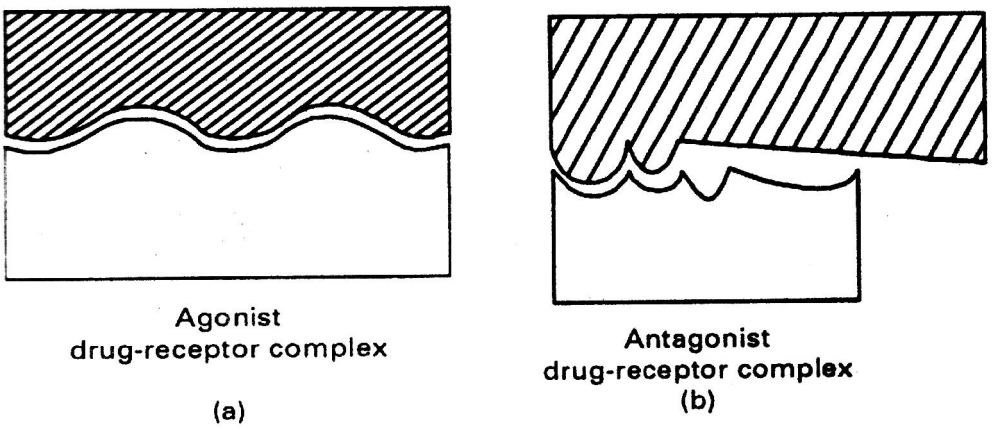


Fig.: An agonist and antogonist drug-receptor complex

Catalytic Receptors An endogenous chemical angiotensin-l, a decapeptide, binds with the enzyme ACE (Angiotensin Converting Enzyme) and is transformed into an octapeptide, called angiotensin-II mainly in the lungs, kidneys and blood vessels. This angiotensin-II is responsible for the increase in blood pressure by vasoconstriction. In persons with hypertension, due to stress, tension, etc., there is an increased production of angiotension-II by the ACE. Therefore, the person develops high blood pressure. Drugs like captopril (13), and enalapril (30), bind with the receptor site of ACE and block it. That is, there is a competition between angiotensin-l molecules and captopril molecules for the receptor site of ACE. As usual, the binding of angiotensin-l with ACE produces angiotensin-II which produces the blood pressure. But, captopril binding to ACE does not produce angiotensin-II. Therefore, overall, the blood pressure is lower now. The captopril drug molecules inhibit the ACE normal function. Drugs like captopril which block the enzyme and prevent its normal catalytic action, are known as enzyme inhibitors.

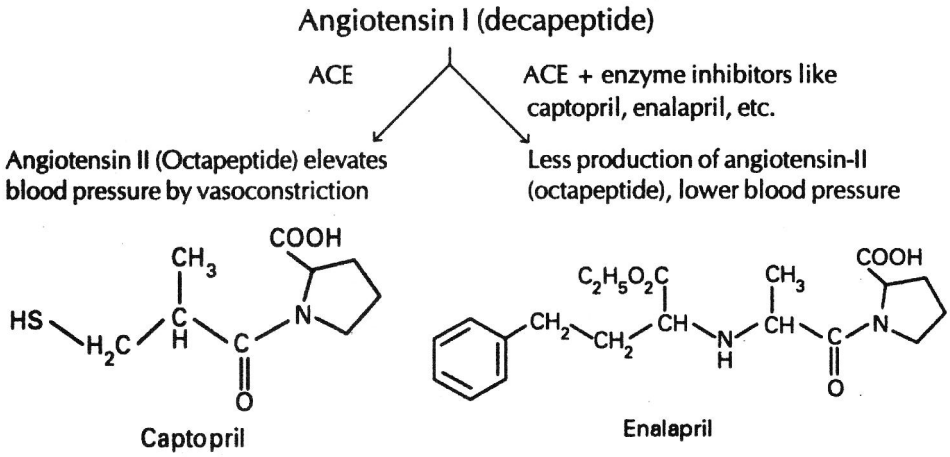


Fig.: Angiotensin-II production

At the site of an injury, inflammation, infection, etc., the enzyme prostaglandin synthase (PGS) assists in the synthesis of prostaglandins. These prostaglandins are responsible for the pain and fever. Drugs like aspirin bind with prostaglandin synthase and block it, and prevent the production of

prostaglandins. This results in anti-inflammatory, analgesic and antipyretic action. Aspirin is the inhibitor of the enzyme prostaglandin synthase.

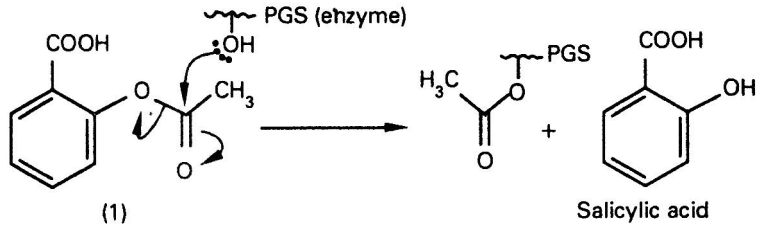
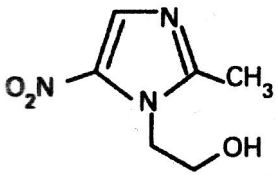


Fig.: Mechanism for inactivation of prostaglandin synthase (PCS) by aspirin

DNA as receptors

Example

In the case of bacterial infections, the drugs are targeted to the proteins or DNA of the bacteria present inside the human body. Penicillin is targeted to the bacterial enzyme Peptidoglycan transpeptidase. This enzyme, which controls the bacterial cell-wall synthesis, is inhibited, leading to the death of the bacteria. Dysentery, whose symptoms include diarrhoea, is caused due to bacterial infections. Metronidazole, a drug to cure dysentery, is targeted at the DNA of the bacteria. This drug attacks the DNA strands, causing bactericidal action.



Metronidazole

Drugs such as ethidium bromide, daunomycin and adriamycin are targeted at the DNA of the tumour cells. This drug molecule is inserted (intercalated) between the double helix of the DNA and thereby prevents its replication. This controls tumour growth.

Q9. Explain about and metabolites antimetabolites.

Ans :

i) Metabolites

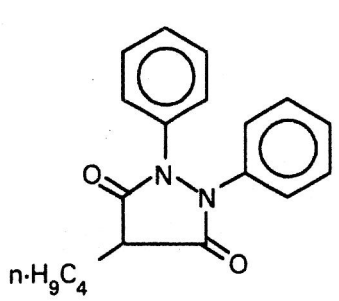
Endogenous chemicals (chemical already present in the human body) as well as drugs are acted upon by a variety of enzymes to give transformed products. These enzyme-mediated transformation products are called metabolites. Metabolites are of two types:

(i) Metabolites produced in the living cells and are useful for the cell functions.

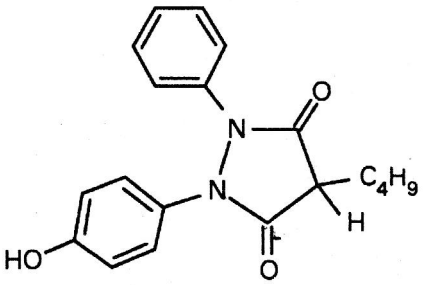
(i) Metabolites produced from the drugs when they are acted upon by enzymes.

These drug metabolites have more, equal or less activity than the original drug. In short, the degraded products of drugs generated in vivo are called drug metabolites. In the process of drug discovery, involves the isolation and screening of the drug metabolites, in order to determine whether the activity observed is due to the drug or its metabolite. The following four examples illustrate the drug metabolites.

(Example 1) The anti-inflammatory drug, phenylbutazone (butazolidine) (8) is converted in the body into its metabolite oxyphenbutazone (33). The metabolite has one new hydroxyl group, which is introduced by the enzymatic transformation.



Phenylbutazone (8)
(Butazolidin)



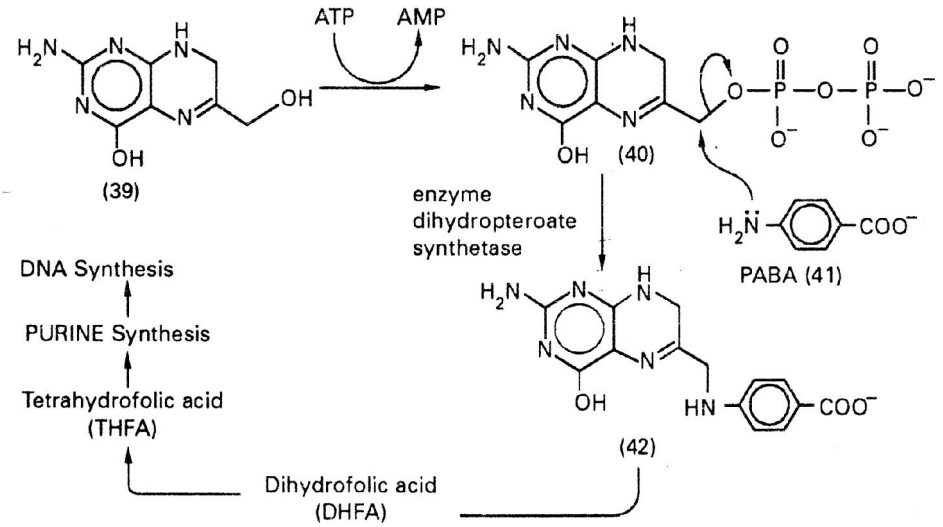
Oxyphenbutazone
(tandearil) (33)
Metabolite of phenylbutazone

ii) Antimetabolites

Antimeatbolites are drugs that mimic the natural substrate (metabolite) of an enzyme. The enzyme involved in a specific biochemical or metabolic pathway is thus inhibited. That is, a metabolite-like drug molecule is incorporated into the endogenous compound. For this reason, further biochemical functions of this drug-incorporated endogenous compound is prevented or disturbed.

In bacteria, the endogenous compound dihydropteridine reacts with Adenosine triphosphate (ATP), and accepts two phosphate groups to transform into dihydrophosphate. In this process, ATP is converted into adenosine monophosphate (AMP) by releasing the necessary two phosphate groups. The dihydropteridine diphosphate combines with the endogenous substrate, or metabolite.

p-amino benzoic acid (PABA), by the action of an enzyme, Dihydropteroate synthetase, to give dihydropteroic acid. This dihydropteroic acid is converted into dihydrofolic (DHFA), which is further transformed into tetrahydrofolic acid (THFA). This THFA is needed for the purine synthesis which, in turn, is necessary for the bacteria DNA synthesis. This is the normal process in bacteria (in the absence of a drug).



Q10. What is therapeutic index.

Ans :

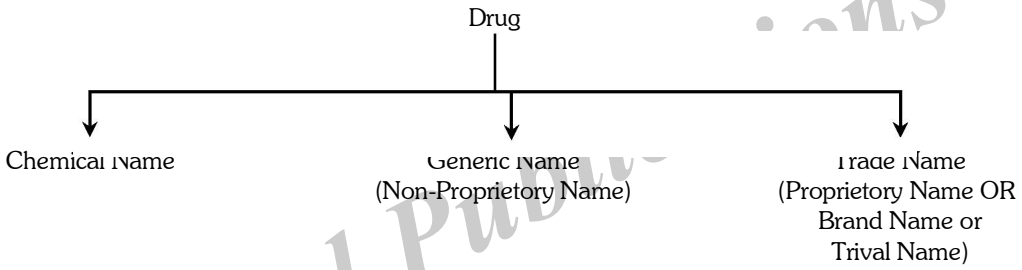
The therapeutic index (TI; also known as therapeutic ratio) is a ratio that compares the blood concentration at which a drug causes a therapeutic effect to the amount that causes death (in animal studies) or toxicity (in human studies)

The therapeutic index (TI; also referred to as therapeutic ratio) is a quantitative measurement of the relative safety of a drug. It is a comparison of the amount of a therapeutic agent that causes the therapeutic effect to the amount that causes toxicity. The related terms therapeutic window or safety window refer to a range of doses which optimize between efficacy and toxicity, achieving the greatest therapeutic benefit without resulting in unacceptable side-effects or toxicity.

Q11. Give the chemical, Generic names & Trade names with examples.

Ans : **(Imp.)**

Medicinal compounds (drugs) normally have more than one name. Every proprietory drug (i.e., a drug which is solid under a trade name) has at least three names - a chemical name, and a trade name.



When the drug first discovered, given a chemical name on the basis of the IUPAC system. The chemical name describes the atomic or molecular structure of the drug.

The generic name is assigned by an official body. In the USA, it is the FDA (Federal Drug Authority) that approves the drug for general prescription. The FDA assigns the generic name to the drug when it is first discovered and developed. Even if the same drug is later marketed by different manufactures, it is known by the same generic name that was first approved of.

The trade name is chosen by the pharmaceutical company that manufactures it. The company tries to choose a unique name that is short and easy to remember. Trade names sometimes link the drug to its intended use or a particular characteristic of the drug. Trade names are also known as proprietory names or trivial names or brand names. A drug manufactured in one country and marketed in other countries may have different trade names in each country.

Individual drugs are almost always referred to by their generic names rather than by their trade or proprietory or brand names. Generally generic (non-proprietory) names have been used. However, because trades names are commonly used and may be more readily recognized, trade names are provided in brackets to several of the generic names mentioned in this book. Some of the generic names are listed along with their trade names.

Generic Name	Trade Name
Amlodipine	Amace
Atenolol	Sectral, Tenormin, Beta card, Atelol, Aten, Betanol
Clofibrate	Atromid-s
Diazepam	Calmpose, Valium
Diltiazem	Cardizen, Dilzen, Diltime
Dichlorphenamide	Daramide

Q12. Classify the drugs based on structures & therapeutic activity with examples.

Ans : **(Imp.)**

Classification of drugs - criteria

Drugs are generally categorized into two groups. They are:

(i) Based on their chemical structure and

(ii) Based on their therapeutic actions.

Chemical structure basis

A similarity in functional groups or ring systems is the basis of this category. Acids, alcohols, phenols, ethers, esters, nitro compounds, amino compounds, amides, amino alcohols, amino ethers, amino acids, carbohydrates, thioureas, alkaloids, and steroids are some of the categories of compounds that are based on a specific functional group or groups and exhibit almost similar properties. Drugs are classified on the basis of similarity in chemical structure. However, in several cases, the chemical structures of the drugs that have similar therapeutic action are so varied that it is difficult to consider them as being strictly in any one of the functional group categories. Also, drugs with similar chemical structure exhibit different therapeutic properties. In spite of these limitations, this classification is useful to study the chemical properties and synthetic routes of the drugs.

Therapeutic action basis

Drugs are classified on the basis of their therapeutic action, into three main classes:

(i) Chemotherapeutic agents

(ii) Pharmacodynamic agents

(iii) Vitamins and Hormones

(i) Chemotherapeutic agents

The word chemotherapy may be defined as the use of drugs in the treatment of infectious diseases, so as to destroy offending parasites or organisms without damaging the host tissues. Drugs which are used to fight the pathogenic organisms are grouped together as chemotherapeutic agents. A pathogen to be killed inside the human body, is an essential prerequisite for any drug to be classified under this category. Based on the disease the pathogen causes, these drugs are further divided into the following categories and the commonly used drugs to combat the diseas are provided alongside them.

Sl. No.	Class of drugs	Disease	Commonly used drugs
1.	Antimalarials	Malaria	Chloroquine, quinine
2.	Antibacterials (sulpha drugs)	Bacterial infection	Sulphanilamide, sulphadiazine
3.	Antibiotics	Bacterial infection	Pencillin G, gentamycin
4.	Antifungals	Fungal	Flucanozole, miconazole
5.	Antiprotozoals	Trypanosomiasis	Metronidazole, suramin
6.	Antihelmentics	Helminths	Niclosamide, quinacrine
7.	Antiseptics	Microorganisms	2-propanol, ethanol, phenol, cresol, resorcinol
8.	Antitubercular drugs	Tuberculosis	Isoniazid, rifampin, streptomycin.
9.	Antileprosy drugs	Leprosy	Dapsone, thiazolsulfone

Table: Chemotherapeutic Agents

(ii) Pharmacodynamic agents

Drugs that alter or regulate the biochemistry of the body are said to be pharmacodynamic agents. Drugs which act selectively on any system of the body like the central nervous system (CNS), peripheral nervous system, cardiovascular system, hematopoietic system, renal system, etc. are refered to as pharmacodynamic agents. These pharmacodynamic agents interact with specific receptors in the body tissues and alter or regulate their biochemical functions. The pharmacodynamic agents are classified, broadly, into the following types of drugs and the site of action of the drug along with the commonly used drugs indicated below.

The relationship between chemical structure and therapeutic actions

The study of the relationship between chemical structure and biological activity involves the synthesis and testing of as many analogs as possible of the lead drug. The task of the medicinal chemist is to improve existing drugs by increasing their efficiency and decreasing their side effects, besides creating new drugs through molecular modifications. The study of structure-activity is of great importance in identifying the pharmacophore.

Sl. No.	Types of drugs	Site of disease	Commonly used drugs
Drugs acting on the central nervous system (CNS)			
1.	CNS depressants (non-selective)	CNS	Morphine, codeine
2.	CNS depressants (selective)	CNS	L-dopa, diazepam, gabapentin
3.	CNS stimulants	CNS	Caffeine, LSD, strychnine
4.	Anaesthetics	CNS	thiopental sodium, chloroform, cyclopropane, butacaine
5.	Antipyretics & Analgesic	CNS	Aspirin, paracetamol, analgin

	Drugs acting on the peripheral nervous system (PNS)		
6.	Antispasmodics	PNS	Atropine, papaverine
7.	Antihistamines	PNS	benadryl, linadryl, antergan
	Drugs acting on the cardiovascular system		
8.	Cardiovascular agents	Heart or blood vessels	Digitalis, lidocaine, reserpine
	Drugs acting on the hematopoietic system		
9.	Anticoagulants	Blood	Heparin, dicoumarol, 4-hydroxy coumarin, warfarin sodium, aspirin
10.	Anti-anemic drugs	Blood	ferrous sulphate, vitamin B_{12}
	Drugs acting on the renal system		
11.	Diuretics	Kidney	bumetanide, chlorothiazide

Table: Pharmacodynamic Agents

The physicochemical properties of the drug molecule such as its lipid solubility, partition coefficient, Pka, etc. Play an important role in the biological activity. A slight modification in the structure may result in a physiologically more active drug with less side effects. The drug action of a molecule is a function of its chemical constitution.

Q13. What is ADMET?

Ans :

ADMET Means

A - Absorption

D - Distribution

M - Metabolism

E - Excretion

Q14. What is Absorption. Give the different routes of administration of drugs.

Ans : **(Imp.)**

A drug is administered by : (i) oral (enteral), (ii) sublingual, (iii) intravenous (parenteral), (iv) intramuscular, (v) subcutaneous,(vi) rectal, (vii) pulmonary, and (viii) topical routes. When the drug is taken orally (the most common and desirable method of administration), it is absorbed mostly through the mucous membrane of the small intestine or the stomach. The small intestine is the principal site for absorption, where most orally administered drugs enter the body. The stomach does not play major role in absorbing drugs, because its area is much smaller than that of the small intestine, and also due to many other factors (the surface area of the small intestines is estimated to be that of single's tennis court!). The degree to which a drug is lipid-soluble and ionized at intestinal pH also influences its absorption in the gut (intestine).

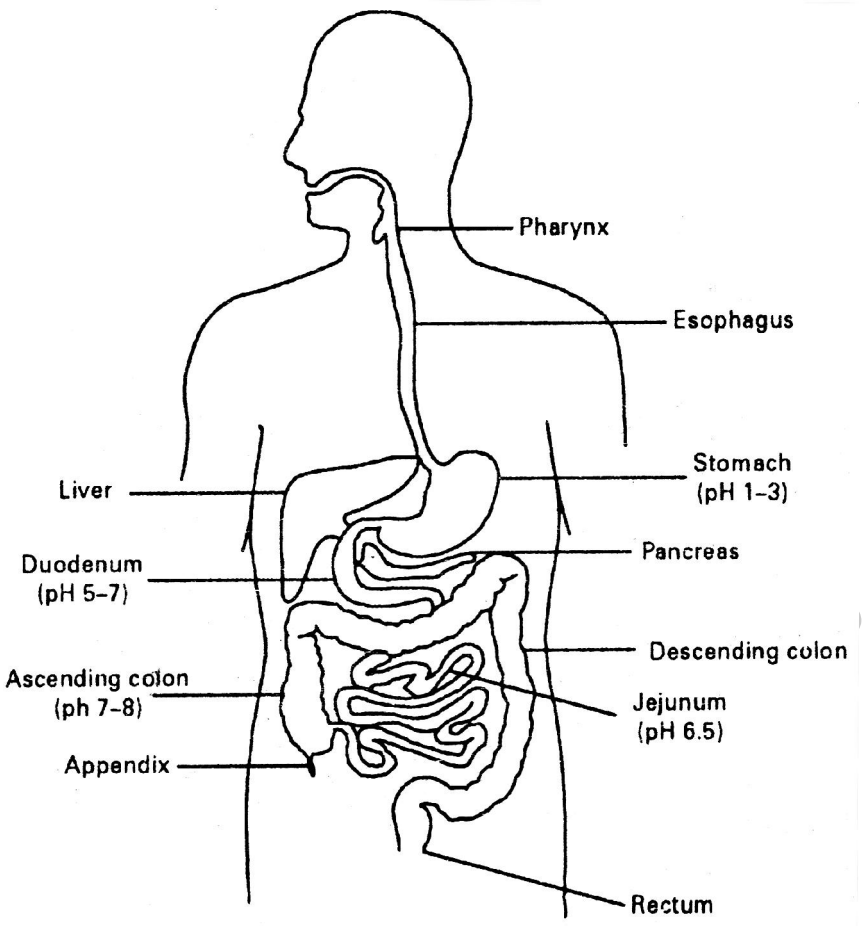
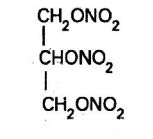
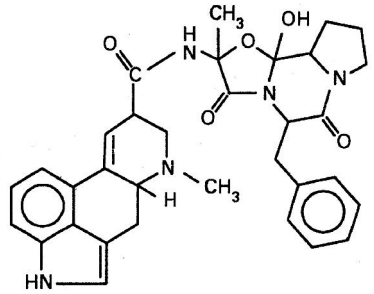


Fig.: Anatomical diagram showing the digestive system including the locations involved in drug absorption, and their respective pHs.

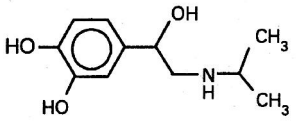
Once out of the gastrointestinal tract, it is carried via the bloodstream to the liver, where it is usually first metabolized. This drug metabolism by the liver enzymes is called the 'first-pass effect'. The first-pass effect can be avoided by changing the route of administration. The sublingual route (the drug placed under the tongue) by passes the liver. After absorption through the buccal cavity, the drug enters the bloodstream directly. This route is used with nitroglycerin, a drug for angina pectoris (a heart condition). An intravenous (i.v.) injection introduces the drug directly into the systemic circulation, and is used when a rapid therapeutic response is desired. The effects are almost immediate when drugs are administered by this route, because the total blood circulation time in humans is about 15 seconds. Intramuscular (i.m.) injections are used when large volumes of drugs need to be administered or if slow absorption is desirable. A subcutaneous injection (s.c.) delivers the drug through the loose connective tissue of the subcutaneous layer of the skin. The rectal route in the form of a solid like a suppository, or in solution as in an enema, leads to absorption through the colon mucosa. Ergotamine, a drug used for migraine headaches, is administered in this way. Another method of administration, particularly for gases or highly volatile drugs, such as anesthetics, is by pulmonary absorption through the respiratory tract. The asthma drug, isporoterenol is metabolized in the intenstines and liver, but administration of salbutamol by aerosol inhalation is effective in getting the drug directly to the lungs. The topical application of the drug to the skin or mucous membrane is used for local effects.



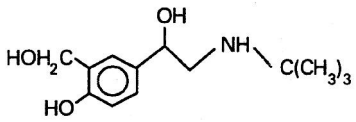
Nitroglycerin (22)
(Glonoin)



Ergotamine (23)



Isoproterenol (24)



Salbutamol (25)

Q15. Define distribution.

Ans :

If a drug is required to act throughout the body or to reach an organ inaccessible to topical administration, Drug must be sent into the blood and into other body compartments. Most drugs distribute widely, some dissolve in plasma water, some bind to plasma proteins, and some to tissues. The distribution is often uneven, as the drugs may bind selectively to plasma or tissue proteins or be localized within particular organs. e.g., iodine in the thyroid.

The site of localization of a drug is likely to influence its action. The pattern of distribution from the plasma to other body fluids and tissues is a characteristic of each and every drug that enters the circulation and it varies enormously between drugs if a drug remains mostly in the plasma, its distribution volume will be small, and it is present mainly in the tissues, its distribution volume will include most of the body, i.e., it will be large. Drugs may also concentrate selectively in a particular tissues because of specialized transport mechanize, e.g., Iodine in the thyroid.

Q16. Explain metabolism in phase I & phase II reactions.

Ans : **(Imp.)**

Metabolism

The enzymatic biotransformation of drugs is known as drug metabolism. Since many drugs have structure similar to those of endogenous compounds, they may be metabolized by specific enzymes. Drugs are treated by the body as foreign substances and various body mechanisms try to defeat the chemical intruders and eliminate them from the body. During the process of metabolism, various steps that take place may have the following effects:

(i) Conversion of a physiologically active drug to an inactive substance. This is the case with most drugs.

(ii) Conversion of a physiologically active drug to another active substance.

E.g.1 Chloroquine → Hydroxy chloroquine

E.g.2 Diazepam → Oxazepam

E.g.3 Amitriptyline → Nortriptyline

(iii) Conversion of a pharmacologically inactive substance to an active drug, i.e., a prodrug.

E.g. 1 Prontosil $\rightarrow$ Sulfanilamide

E.g. 2 L-Dopa $\rightarrow$ Dopamine

E.g. 3 Talampicillin $\rightarrow$ Ampicillin

A number of tissues, including the kidney, gut mucosa (gastrointestinal tract), lung and skin metabolize drugs, but the liver is by far the most important site, as many enzymes are present here. Drug metabolism reactions have been divided into two general categories termed as "Phase-I" and Phase-II" reactions.

Phase I

Phase I metabolism brings about a change in the drug molecule by oxidation, reduction or hydrolysis, and often introduces a reactive functional group into it. These reactions are catalyzed by enzymes.

For example

Oxidation - Propranolol is oxidized to hydroxy propranolol

Reduction - Nitrofurazone is reduced to 5-hydroxylamino derivative.

Hydrolysis - $COOCH_3$ gp is hydrolyzed to -COOH in the case of Cocaine (5).

Phase II

In Phase II conjugating enzymes catalyze the attachement of small polar endogenous molecules such as glucuonic acid, sulphate, and amino acids to drugs or, more often, to metabolites of Phase-I enzymes. This further deactivates the drug and produces highly water-soluble metabolites that are readily excreted in the urine or in the bile.

Q17. Define elemination.

Ans :

Drugs are eliminated from the body either unchanged or as metabolites. Generally, the more polar drugs are excreted readily. The less polar, lipid-soluble drugs, however, are not readily eliminated until they are metabolized to more polar, less lipid-soluble compounds. The kidney is the most important organ for drug excretion in the form of urine. Drugs excreted in the faeces are derived either from unabsorbed, orally-injested drugs or from metabolites excreted in the bile. Pulmonary excretion is of importance mainly for the elimination of anesthetic gases and vapours.

Q18. Write about toxicity.

Ans :

The degree to which a substance (a toxin or poison) can harm humans or animals. Acute toxicity involves harmful effects in an organism through a single or short- term exposure.

Toxicity is the degree to which a chemical substance or a particular mixture of substances can damage an organism. Toxicity can refer to the effect on a whole organism, such as an animal, bacterium, or plant, as well as the effect on a substructure of the organism, such as a cell (cytotoxicity) or an organ such as the liver (hepatotoxicity).

Short Question and Answers

Q1. What is Diseases ?

Ans :

Disease can be defined as an endogenous biochemical imbalance, an abnormal and aberrant proliferation of cells, or an exogenous chemical toxin or an invasive pathogen in the body.

Q2. Define drug.

Ans :

A drug is defined as an agent intended for use in the diagnosis, mitigation, treatment, cure or prevention of disease in man or in other animals. According to World Health Organisation (WHO), who promote basic health globally, "A drug is any substance or product that is used or intended to be used to modify or explore physiological systems or pathological states for the benefit of the recipient."

Q3. Give the standard name of API and define it.

Ans :

Active pharmaceutical ingredients (APIs) are the active components in a pharmaceutical drug that produce the required effect on the body to treat a condition. APIs are produced by processing chemical compounds.

Q4. Write about pharmaceuticals.

Ans :

The pharmaceutical industry discovers, develops, produces, and markets drugs or pharmaceutical drugs for use as medications to be administered to patients (or self-administered), with the aim to cure them, vaccinate them, or alleviate symptoms.

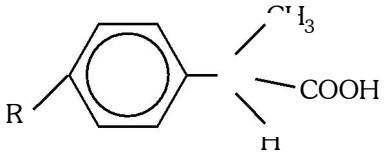
5. What is pharmacophore give example.

Ans :

Pharmacophore

The parts of the drug molecule that interact with the receptor and are responsible for biological activity are known as the pharmacophore of the compound. Any structural alterations of the pharmacophore from the molecule of a drug either lessens or totally destroys its medicinal value.

The common structural feature in all the three anti-inflammatory drugs is aryl methylacetic acid.



The molecular fragment which binds with the receptor and is responsible for its biological action, is called the pharmacophore of the drug. Therefore, the pharmacophore is related to the pharmacodynamics

of the drug. The other part of the drug molecule is commonly called the non pharmacophore of the drug. The non-pharmaco-phore mostly decides the pharmacokinetics of the drug. Changes in the molecular structure of the pharmacophore part lead to the loss of a specific drug property, while changes in the nonpharma cophore part may not change the drug properties.

6. What is therapeutic index.

Ans :

The therapeutic index (TI; also known as therapeutic ratio) is a ratio that compares the blood concentration at which a drug causes a therapeutic effect to the amount that causes death (in animal studies) or toxicity (in human studies)

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Ans :

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M - Metabolism

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8. Define distribution.

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10. What are Metabolites

Ans :

Endogenous chemicals (chemical already present in the human body) as well as drugs are acted upon by a variety of enzymes to give transformed products. These enzyme-mediated transformation products are called metabolites. Metabolites are of two types:

(i) Metabolites produced in the living cells and are useful for the cell functions.

(i) Metabolites produced from the drugs when they are acted upon by enzymes.

These drug metabolites have more, equal or less activity than the original drug. In short, the degraded products of drugs generated in vivo are called drug metabolites. In the process of drug discovery, involves the isolation and screening of the drug metabolites, in order to determine whether the activity observed is due to the drug or its metabolite. The following four examples illustrate the drug metabolites.

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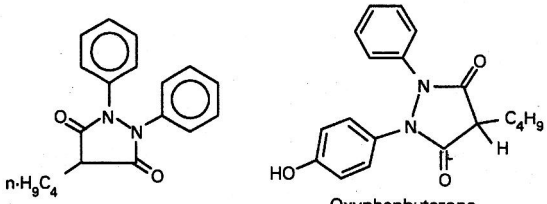


11. Write about of Renalelimination.

Ans :

Renal Excretion

Renal excretion completes the process of the elimination that begins in the liver. Polar drugs of or thier metabolities get filtered int he kidneys and typically do not undergo reasborption. They subsequently get excreted int he urine.

Renal elimination of these drugs reflects and depends on neonatal renal function. Which is characterized by alow glomerular filteration rate (GFR). Low effective renal blood flow, and low tubular function (secretion and reabsorption) compared with that in the adult.

Glomerular Filtration

Free drug flows out of the body and into the urine-to-be as part of the glomerular filtration.

12. Reabsorption excreation by filteration.

Ans :

- **Glomerular Filtration:** Free drug flows out of the body and into the urine-to-be as part of the glomerular filtration.
- **Proximal tubular secretion:** Some drugs are actively secreted into the proximal tubule.
- **Distal Tubular Reasborption:** Uncharged drugs may diffuse out of the kidney and escape elimination.

Choose the Correct Answers

1. The molecular fragment which is responsible for biological action is [c]
   (a) Pharmacodynamic agent (b) Receptor
   (c) Pharmacophore (d) Metabolite
2. The biological macromolecule in human body with which the drugs bind to the drug action is called as _____. [b]
   (a) Pharmacophore (b) Receptor
   (c) Metabolite (d) All the above
3. A qualitatative measurement of the relative safety of a drug is _____. [b]
   (a) Metabolism (b) Therapeutic index
   (c) Renal elimination (d) None of the above
4. Drugs which are used to fight the pathogenic organism are grouped together known as _____ [a]
   (a) Pharmacodynamic agents (b) Pharmacokinetic agents
   (c) Chemotherapeutic agents (d) All the above
5. _____ is the most important organ for drug excretion. [d]
   (a) Heart (b) Pancreas
   (c) Lungs (d) Kidney
6. A substance or product is used to modify or explore physiological systems for the benefit of the recipient is known as [b]
   (a) Pharmacophore (b) Metabolite
   (c) Drug (d) Antimetabolite
7. The deficiency of iron results in _____ [a]
   (a) Anemia (b) High blood pressure
   (c) Cholera (d) None of the above
8. The sudden heritable change of a gene in an organism is known as [a]
   (a) Anemia (b) Pernicious anaemia
   (c) Mutation (d) Transformation
9. The instrument used to measure blood pressure is [a]
   (a) Sphygmomanometer (b) Colorimeter
   (c) p^H meter (d) All the above
10. The metal ion necessary for flood clotting is [a]
   (a) Ca^{+2} (b) Mg^{+2}
   (c) Al^{+3} (d) All the above

Fill in the Blanks

1. API means _____.
2. The part of the drug molecule interact with the receptor are responsible for biological action are called as _____.
3. The study of Adsorption, distribution, metabolism, excretion of drugs known as _____.
4. The enzyme mediated transformation products are called _____.
5. Drugs alter or regulate the biochemistry of the body are said to _____.
6. Drugs acting on renal system are called as _____.
7. The enzymatic biotransformation of drugs is known as _____.
8. Drug - Receptor binding responsible for _____.
9. The study of interaction of the drug with the receptor is known as _____.
10. The drugs mimic the natural substrate of an enzyme are _____.

ANSWERS

1. Active pharmaceutical ingredient
2. Pharmacophore
3. Pharmacokinetics
4. Metabolites
5. Pharmacodynamic agents
6. Diuretics
7. Drug metabolism
8. Biological response
9. Pharmacodynamics
10. Antimetabolites

UNIT - II

(Medicinal Chemistry)

Enzymes and Receptors

S6-E-A-II: Enzymes: Introduction. Mechanism and factors affecting enzyme action, Specificity of enzyme action (including stereo specificity), Enzyme inhibitors and their importance. Types of inhibition - reversible, irreversible and their subtypes with examples.

Receptors: Introduction, Drug action-receptor theory, Mechanism of drug action, concept of agonists and antagonists with examples. Drug receptor interactions involved in drug receptor complex, binding role of –OH group, $–NH_2$ group, quaternary ammonium salts and double bond. Structure – activity relationships of drug molecules, explanation with sulfonamides.

S6-E-A-II: ENZYMES

Q1. What are enzymes?

Ans :

Enzymes can be defined as soluble, collodial, organic catalysts which are produced by living cells but are capable of acting independently of the cells. Most enzymes are protein in nature and exhibit all properties of the proteins. They are water soluble; precipitated by the usual protein precipitating reagents like alcohol, ammonium sulfate and alkaloidal reagents; they are non-dialyzable, amphoteric, have isoelectric points and have a nitrogen content of about 16%. Extreme alterations of pH and high temperatures denature the enzyme protein and thus make it inactive.

Q2. Write the factors affecting enzyme action.

Ans : **(Imp.)**

Physical Factors Altering Enzyme Activity

The action of various factors like temperature, concentration of the enzyme, substrate etc., can all be explained on the basis of kinetic theory or collision theory. For any reaction to occur, two conditions have to be satisfied: (i) the reacting molecules will have to collide with each other. All molecules above the absolute temperature (–273^0 C) are in perpetual motion. The molecular movement increases with rise in temperature. A rise in temperature also increases the kinetic energy of the molecules. Increasing the concentration of the reactant molecules, likewise, will increase the chance for collision between the molecules; (ii) the reactant molecules must have sufficient energy to overcome the energy barrier for the reaction. Enzymes are said to lower this energy barrier and initiate the reaction.

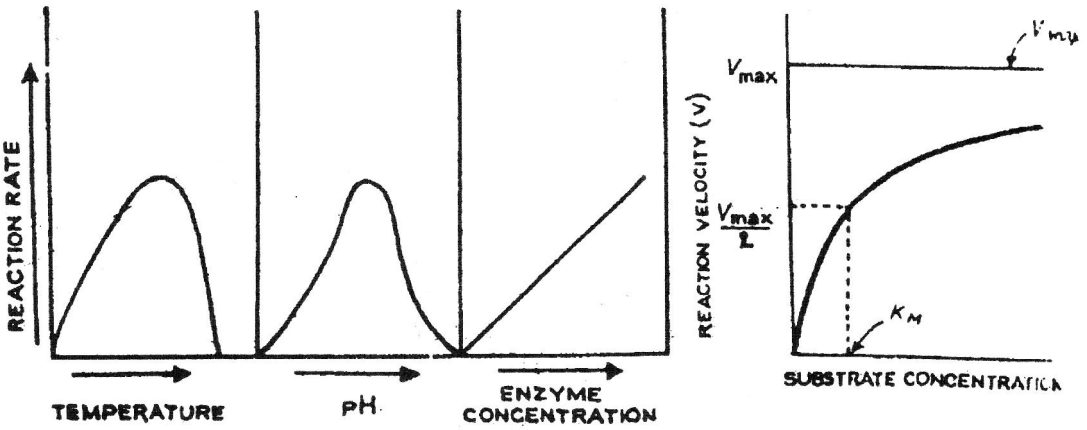


Figure : Factors affecting enzyme activity

1. Contact between the enzyme and substrate:

The enzyme being a protein forming a colloidal solution, the substrate also must be a water soluble substance. If the substrate is a lipid, it must be emulsified to enable it to come into contact with the enzyme. Thus pancreatic lipase can act on lipids in the gastrointestinal tract only when the lipid is emulsified by bile salts. In obstructive jaundice where bile is absent in the intestinal tract, fat is excreted in feces undigested.

2. Concentration of the substrate

Keeping all the other things constant, an increase in the substrate concentration increases the enzyme activity till a maximum is reached. Further increase in substrate concentration does not increase rate of reaction. The phenomenon is explained thus-as concentration of substrate is increased, the substrate molecules combine with all available enzyme molecules at their active sites and no more active sites are available. Once this stage is reached, substrate is required only to replenish the sites when the products are liberated and can-not increase the rate of reaction further.

The Michaelis Menton Constant

It is possible to mathematically evolve a relation between the substrate concentration and the velocity of reaction.

$$v = \frac{V(S)}{Km + (S)}$$

Where

v = Velocity at a given concentration of substrate.

V = Maximal velocity possible with excess of substrate.

(S) = Concentration of the substrate at velocity v.'

K_m = Michaelis constant for the enzyme.

It is possible to so choose (S) as to make v = 1/2 V.

Then $V/2 = \frac{V(S)}{K_m + (S)}$

dividing by V

$$\therefore \quad 1/2 = \frac{V(S)}{K_m + (S)}$$

$$\therefore \quad K_m + (S) = 2(S)$$

$$\therefore \quad K_m = (S)$$

Hence K_m, the Michaelis constant, can be defined as the concentration of the substrate when the velocity of the enzyme reaction is half the maximal possible. The K_m value varies from enzyme to enzyme and is used in characterizing the different enzymes.

A high K_m value indicates weak binding between the enzyme and the substrate, whereas a low K_m indicates strong binding.

3. Concentration of the enzyme

Within reasonable limits, the initial rate of an enzyme reaction is directly proportional to the concentration of the enzyme. In course of time, due to accumulation of products of the reaction and the tendency for the reaction in the reverse direction, the rate of enzyme reaction diminishes. shows the reaction-enzyme relations immediately on addition of the enzyme.

4. Concentration of the products

Accumulation of products of reaction causes a lowering of the enzyme activity. This is prevented in nature by prompt removal of the products from the site of formation, e.g.absorption of the products of digestion from gastrointestinal tract into the blood stream.

5. pH

Some enzymes act best in an alkaline medium; others in an acid medium. For every enzyme there is a pH where it acts at its best and this is its optimal pH. The optimum pH for pepsin is around 2.0 while that of trypsin varies from pH 8.0 to 9.0. It is probable that pepsin attacks the substrate molecules best if they carry a positive charge while trypsin attacks the negatively charged substrate molecules. For most biological enzymes the optimum pH is around 7.4.

6. Effect of temperature

All chemical reactions get accelerated with rise in temperature, whether mediated by catalyst or not. In case of enzyme activity also this holds good up to a certain increase in temperature (say 50^0C). Above that temperature, another process-namely the denaturation of the enzyme protein sets in and rapidly decreases the enzyme activity annulling the general beneficial effect of heat on chemical reaction. The enzyme reactions altogether cease at a temperature if 70 to 80^0C. If the temperature is further raised, the enzyme becomes totally denatured and remains inactive even if temperature is brought down subsequently. This is an important means of distinguishing an enzyme catalyzed reaction from other catalytic reactions. All catalytic activity is lost on boiling, if catalysis is enzymic.

An enzyme becomes less active when cooled and is altogether inactive at 0^0C. But the activity is regained if the temperature is raised again. Thus it is a reversible inactivation. Enzymes can be stored for years by keeping in a frozen state. They regain full activity if they are brought back to laboratory temperature.

The temperature at which an enzyme shows maximum activity is known as the optimum temperature for the enzyme. For most animal enzymes it is around the body temperature 37^0C. Some plant enzymes like urease have higher optimum temperature even up to 60^0C.

Temperature coefficient-Q10

The ratio of the reaction rate at temperature t + 10^0C to that at t is known as the temperature coefficient and is usually 2. That means the rate of reaction is double the initial rate when the temperature is increased by 10^0C.

7. Effect of oxidizing substances

The activity of many enzymes, particularly the hydrogenases, depends on –SH groups. The activity is lost if the –SH groups are oxidized to –S–S– groups. Reducing substances like glutathione and cysteine can reactivate such enzymes.

8. Radiation

Exposure to ultraviolet rays, X-rays, beta and gamma rays causes the formation of peroxides which oxidize the enzymes and make them inactive. This is an immediate effect. In addition, they exert effects on the DNA molecules (gene) which will lead to impaired synthesis of the enzymes as a delayed effect.

Q3. Mention the enzyme specificity.

Ans :

Enzyme Specificity

Specificity is a characteristic property of the active site.

1. Stereospecificity or optical specificity

Stereoisomers are the compounds which have the same molecular formula differ in their structural configuration.

The enzymes act only on one isome.

Ex: L-amino acid. Oxidase and D-amionacid oxidase act on L- and D-aminoacids. Hexokinase on D-glucose amylase acts on α - glycosidic linkages, cellulose cleaves β - glycosidic bond.

Stereospecificity is explained by considering three distinct region of substrate molecule specifically binding with three complementary regions on the surface of the enzym. The ezymes belonging to isomerases do not exhibit stereospecificity.

2. Reaction specificity

The same substrate can undergo different types of reaction each catalysed by a seperate enzyme. and this is referred to as reaction specificity. An Amino acid can undergo transamination.

3. Substrate specificity

The substarte specificity varies from enzyme to enzyme. It may be either absolute, relative or broad.

Absolute substrate specificity certain enzymes act only on one substrate eg: Glucokinase acts on glucose to give glucose-6-phosphate, urease cleaves area to ammonia and carbondioxide.

Q4. Discuss the enzyme inhibitors and their importance.

Ans : **(Imp.)**

Enzyme Inhibition

1. Irreversible or non-competitive inhibition:

Many enzymes like papain, urease and succinic dehydrogenase require for their activity the presence of free –SH groups in their molecules. The addition of glutathione, cysteine, H_2S and traces of HCN activate such enzymes by preventing oxidation of the –SH group. Compounds like iodoacetate and P-chloromercuribenzoate (PCMB) combine with –SH groups and thus inactivate the enzymes. Heavy metals like Ag^+, Hg^{++} also combine irreversibly with the –SH groups and inactivate enzymes. Some enzymes which require metallic ions for their activity are inhibited by chelating agents like ethylenediamine tetraacetate (EDTA).

Di-isopropylfluorophosphate (DFP) inhibits acetylcholinesterase by combine with a serine residue at the active site of the enzyme. Transmission of nerve impulses is blocked leading to paralysis.

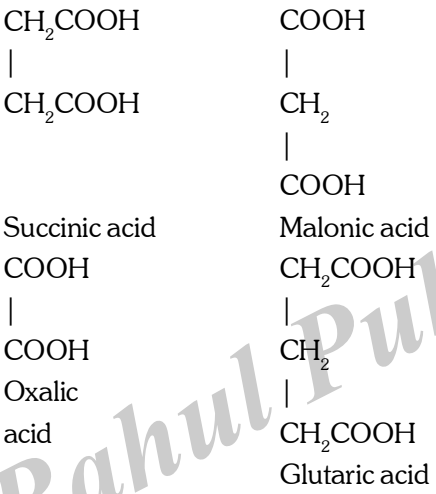
This type of inhibition is irreversible and will make the active site of the enzyme ineffective. Addition of any amount of the substrate does not restore activity.

2. Reversible or competitive inhibition:

The pharmacological action of several drugs is dependent on the ability of the drugs to inhibit one or other of the enzymes responsible for the growth and multiplication of microorganisms. The inhibitor, which has close structural resemblance to the substrate, competes with the substrate for the active or binding sites and thus diverts much of the enzyme to form the enzyme-inhibitor complex instead of enzyme-substrate complex. The enzyme-inhibitor complex does not yield any products and hence remains stable, thus preventing further enzyme activity. This type of an inhibition can be reversed by adding excess of substrate which will successfully dislodge the inhibitor molecules from the enzyme.

Some examples of competitive inhibition are considered below:

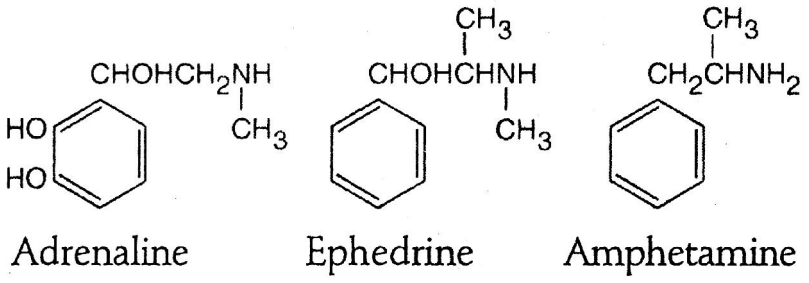
(i) Succinic dehydrogenase can be inhibited by malonate, oxalate and glutarate, all of which resemble the substrate, succinic acid, in structure.



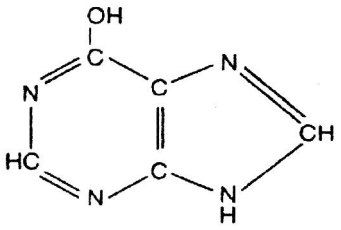
(ii) Monoamine oxidase (MAO) oxidizes pressor amines like adrenaline and noradrenaline.

Ephedrine and amphetamine, which have similar structure as adrenaline and noradrenaline, inhibit the enzyme and thus prolong the action of the pressor amines.

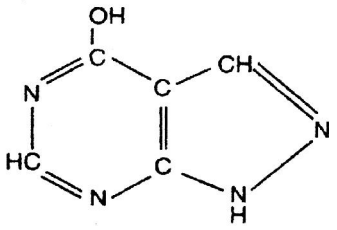
Cheese contains large amounts of tyramine. The oxidation of tyramine also requires MAO. By decreasing the availability of MAO for adrenaline oxidation, cheese also prolongs adrenaline action.



(iii) In gout, uric acid accumulates in tissues, and causes symptoms. Uric acid is formed by oxidation of hypoxanthine by xanthine oxidase. Allopurinal has a structural resemblance to hypoxanthine and by competitive inhibition decreases formation of uric acid.



Hypoxanthine



Allopurinol

(iv) Higher animals as wells as microorganisms require certain natural substances like vitamins, amino acid, purines, pyrimidines, etc., which are used as such or after incorporation into other macromolecules. The utilization of these metabolites is dependent on enzymes. The enzymes may be inhibited by substances which have a structural resemblance to the metabolites. The inhibitors are called "antimetabolites", and the type of inhibition is competitive.

Some of these antimetabolites are produced by living organisms like bacteria, fungi, etc., and are then called "antibiotics" e.g. penicillin, streptomycin, chloramphenicol and tetracycline.

Q5. Classify the enzyme inhibitors and write the examples.

Ans : **(Imp.)**

Enzyme Inhibition

Enzyme Inhibitor is defined as a substance which binds with the enzyme and brings abart a decrease in catalytic activity of that enzyme. The inhibitor may be organic or inorganic in nature.

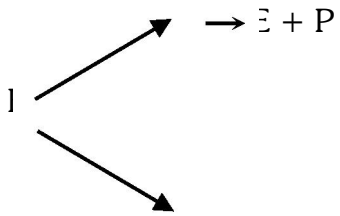
1. Reversible Inhibition
2. Irreversible Inhibition

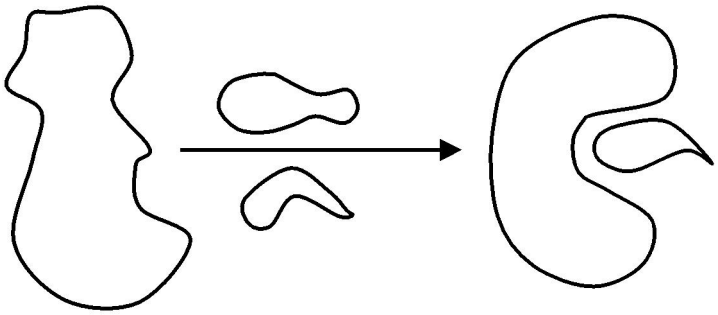
1. Reversible Inhibition

The inhibitor binds noncovalently with enzyme and the enzyme inhibition can be reversed if the inhibitor is removed. The reversible inhibitor is further sub divided into

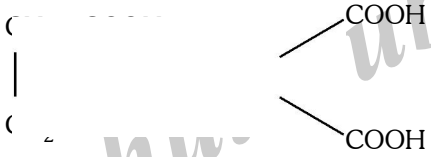
Competitive inhibition

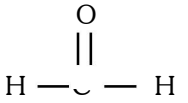
The inhibitor which closely resembles the real substrate is regraded as substrate analogue. The inhibitor competes with substrate and binds with the active site of the enzyme but does not undergo any catalysis. As long as the competitive inhibitor holds the active site the enzyme is not available for the substrate to bind. During the reaction ES & EI complexes are formed





The inhibition could be overcome by a high substrate conc. The k_m value Tses V_{max} remains unchanged.



Methanol is toxic to the body when it is converted to  by the enzyme alcohol dehydrogensae (ADH) Ethanol can compete with methanol for ADH. Ethanol can be used in the treatment methanol poisoning.

Non - competitive inhibition

The inhibitor binds at a site other than the active site on the E surface. This binding impairs the E function. The inhibitor has no structural resemblance with the substrate.

$$E + S \rightleftharpoons ES \rightarrow E + P$$

$$\downarrow \qquad \downarrow$$

$$I \qquad I$$

$$\uparrow V \qquad \downarrow L$$

$$EI + S \qquad EIS$$

For non-competitive inhibition km is unchanged V_{max} is lowered.

$$E - SH + Hg^{2+} \rightleftharpoons E - S \ldots Hg^{2+} + H^{+}$$

Uncompetitive inhibition.

This is known as anti-competitive inhibition. The I binds to the Eg. complex and not to the free enzyme. Both K_m & Vmax an uncompetitive inhibitor need not have any structural resemblance with the substrate.

Ex. Inhibition of placental alkaline phosphatase by phenylalanine.

2. Irreversible Inhibition

The inhibitor bind covalently with the enzyme and inactivate them. These inhibitors are usually toxic substance that position enzymes.

Many organophosphorus insecticides like melathion are toxic to animals they block the acetylcholne esterase (essential for nerve conduction).

Relative substrate specificity

Enzymes act on structurally related substances. The action of trypsin is a good example for group specificity. Trypsis hydrolysis peptife linkage involving arginine or lysise. Chymotrypsin cleaves peptide bonds attached to aromatic amino acids. Bond specificity glycosidases acting on glycosidic bonds of carbohydrates, lipases cleaving bonds of lipid etc.

Broad specificity

Enzymes act on closely related substrate which is commonly known as broad substrate specificity eq. hexokinase acts an glucose, fructose, mannose and glucosamine and not an galactose. Some structural similarity among the first four compounds make them a common substrate for the enzyme hexokinase.

Q6. What are Receptors.

Ans :

A receptor is a protein molecule that receives chemical signals from outside a cell. When such chemical signals bind to a receptor, they cause some form of cellular/tissue response, e.g. a change in the electrical activity of a cell.

Receptors are protein molecules inside the target cell or on its surface that receive a chemical signal.

Q7. Explain the Drug action - receptor theory.

Ans : **(Imp.)**

Ligands and receptors exist in several varities; however, a specific ligand will have a specific receptor that typically binds only that ligand.

Most receptors are membrane-bound proteins that contain an external binding site for hormones or neurotransmitters.

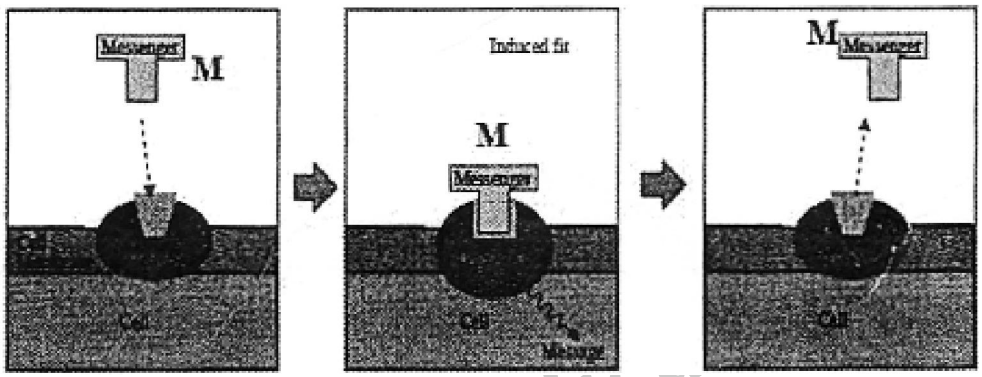
Binding results in an induced fit that changes the receptor conformation. This triggers a series of events that ultimately results in a change in cellular chemistry.

Neurotransmitters and harmones do not undergo a reaction when they bind to receptors. They depart the binding site unchanged once they have passed on their message.

The interactions that bind a chemical messenger to the binding site must be strong enough to allow the chemical message to be received, but weak enough to allow the messenger to depart.

Binding groups are the functional groups present on a messenger molecule which are used for binding it to be the receptor binding site.

Binding regions are the receptor binding site which contain functional groups capable of forming intermolecular bonds to the binding groups of a messenger molecule.



Structure and function of receptors mechanism

Receptor ligands can be distinguished on the basis of their potential to initiate a biological response following receptor binding:

There are four main types of receptors that act as drug targets:

a) Ion channels : Which can open or close in response to the drug binding.

b) Enzyme-coupled receptors: Receptors on the outer surface of cell membranes which can activate enzymes on the interior surface of the membrane.

c) G protein-coupled receptors (Adrenergic receptors): Receptors on the outer surface of cell membranes that can activate G protein on the interior surface of the membrane. These in turn activate enzymes, which produce chemical messengers such as cyclic AMP.

d) Receptors within the cell, for example sites in the nucleus which controltranscription.

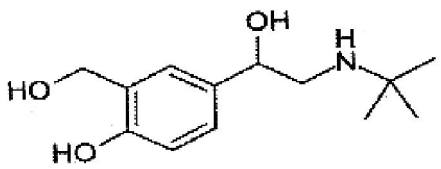
1. These receptor molecules all have a specific role in the control of cellular processes and there are naturally occuring ligands that bind to the receptor molecule, forming a ligand-receptor complex. Ligands usually have a complementary structure to the receptor site, so this is a very similar situation to the enzyme substrate mechanism discussed in the previous section.

2. Many drug molecules acts as ligands for a range of receptor sites which explains the wide range of physiological effects produced by some drugs.

Agonists bind to a receptor protein to produce a conformational change, which is necessary to initiate a signal that is coupled to a biological response. As the free ligand concentration increases, so does the proportion of receptors occupied, and hence the biological effect. when all of the receptors are occupied the maximum biological effect is achieved. It has been observed in many receptor systems that full agonists can elicit the maximum effect without occupying all available receptors, suggesting the concept of 'spare receptors'. This apparent excess of receptors allows full responses to occur at lower ligand concentrations than would otherwise be required.

Antagonists bind to a receptor but do not produce the conformational change that initiates an intracellular signal. Occuption of the receptor by a competitive antagonist prevents binding of other ligand and so 'antagonizes' the biological response to the agoinst. The inhibition that antagonists produce can be overcome by increasing the dose of the agoinst. Some antagonists interfere with the response to the agoinst in other ways than receptor competition and are known as non-competitive antagonists. Simply increasing the dose if the agonist cannot overcome their effects and so the maximum response to the agonist (its 'efficacy') is reduced.

E.g., Mechanism action of an Agonist drug Salbutanol



Examples of drugreceptor interactions:

Drug name	Used to treat	Mechanism of action	Agonist or agntagonist
Nifedipine	Hypertension Angina,	Binds to ion channel protein on surface of smooth muscle cells, preventing calciumions from crossing membrane and altering electrical potential of cell.	Antagonsit
Salbutanol	Asthma	Binds to recognition site on surface of membrane. This activates the G protein on the internal surface, stimulating AMP production.	Agonist

Q8. Define agonists mention the types of agonists.

Ans : **(Imp.)**

An agonist is a drug that interacts with a receptor and produces an observable biological effect similar to that of endogenous substance (adrenaline).

Adrenaline is an endogenous substance which binds to the β adrenergic receptor of bronchioles in lungs leading to the brancheo dilation.

If there is less adrenaline in the body it leads to symptoms of asthma.

Salbutamol is an β adrenergic agonist drug has structural similarities with the adrenaline, binds to the receptor causing brancheo dilation similar to that produced by adrenaline.

It is used to treat asthma and branchiole asthma, lung diseases.

It selectively binds adrenergic receptors; the natural neuro transmitter noradrenaline sufficiently releases bronchiole expansion and contraction happens smoothly but when noradrenaline secretion was reduced bronchioles were contracted.

When, an agonist drug inhaled by the living system which the role which carries similar to noradrenalin and effective function of lugs i.e expansion and contraction takes place.

Partial agonists are able to activate a receptor but cannot produce a maximal signalling effect equivalent to that of a full agonist even when all available receptors are occupied. When mixed with full agonist, partial agonists block receptor sites that could potentially be occupied by the full agonist, which reduced the overall response (i.e. they seem to antagonize the effect of the full agonist).

Partial agonists have some advantaged as therapeutic agents. Although they are unable to achieve the same maximum effect as the full agonist, they are less likely to produce receptor-mediated adverse effects at the top of their dose-response curve (e.g. the partial opioid receptor agonist buprenorphine does not cause as much respiratory depression as morphine when it is used as an analgesic).

Inverse agonists produce the opposite effect to the full agoinst when they bind to a receptor. For inverse agonists to be identified, the revelant endogenous receptor must show some degree of coupling to a biological response even in the absence of ligand binding (i.e. constitutive activity). Many receptors posses constitutive activity.

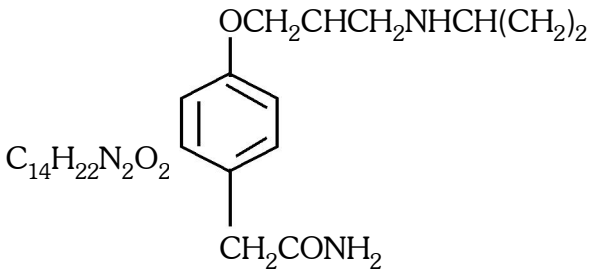
Q9. Define Antagonists.

Ans :

Antagonists

A drug molecule may bind to the receptor site without causing aresponse. If, by binding in this way, the drug prevents further ligands binding (byblocking the site or causing a conformational change) then the drug molecule is known as an antagonist.

E.g. Mechanism action of an Antagonist drug Atenolol



These are β adrenergic antagonist and acts as antihypertensive agent use to treat arrhythmia (abnormal heart beat). When these drugs bind to β adrenergic causes dilation of blood vessels relaxation of heart muscle causes the decreased cardiac output, slow down the heartbeat, reduces the force of the attack in heart.

Longer usage may cause brancheo contraction causes asthma.

Atenolol is the cardio selective, β receptor blocker antihypertensive agent and longer duration of action available as tablet forms 5 to 25 mg.

Q10. Mention the drug receptor interactions involved in drug receptor complex.

Ans : **(Imp.)**

Drug receptor interactions involved in drug receptor complex

Drug-Receptor Interactions involve all known types of bond:

Ionic Bonding Interactions

1. Ionic bonds are formed between ions of opposite charge.
2. Their electrostatic interactions very strong with a bonding energy (E) that can approach or even exceed the energy of a covalent bond.
3. Ionic bonds are ubiquitous and, since they act across long distances, play an important role in the actions of ionizable drugs.
4. The interaction between a negatively charged carboxylate and a positively charged ammonium is a prototypic example of anionic interaction.

Covalent Bonding Interactions

1. Covalent bonds are lessim portant in drug-receptor binding than non-covalent interactions.
2. It is generally not desirable to have a drug covalently linked to its receptor, since such an interaction would persist for a long period of time.
3. Such prolonged interactions tend to lead to difficulties with lengthy drug half-lives and potentially to toxicity problems.
4. Accordingly, the only receptors to which covalent binding is desirable are those that belong to exogenous.
5. Drugs with short duration of action generally have weaker bonds, long duration or irreversible drug receptor interactions may have stronger bonds such as covalent.

   e.g., Pencilline

Dipole Dipole Interactions

1. Molecules in which there is a partial charge seperation between adjacent atoms or functional groups can interact either with each other (via a dipole-dipole interaction) or with ions.
2. Dipole moments are bond moments resulting from charge differences and the distance between charges with in a molecule.

3. A carbonyl (C=O) functional group, constitutes a dipole since the carbon is electropositive and the oxygen is electronegative.

Vander Waal Bonding Interactions

1. The distance between atoms at which the force becomes repulsive rather than attractive as the atoms approach one another is called the vander waals contact distance.
2. This phenomenon results from the mutual repulsion between the atoms electron clouds.
3. The term vander waals force is sometimes used loosely for all intermolecular forces.

Hydrogen Bonding Interactions

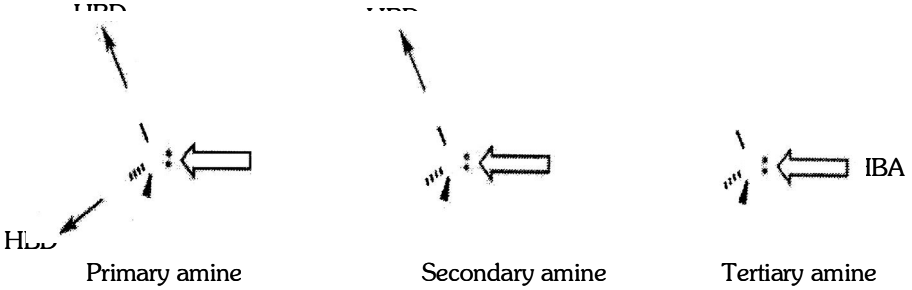
1. Hydrogen bonding is based on an electrostatic interaction between the non bonding electron pair of a heteroatom (N, O, and even S) as the donor, and the electron-deficient.
2. Hydrogen atom of –OH, –SH, and –NH groups.
3. Hydrogen bonds are strongly directional, and linear hydrogen bonds are energetically preferred to angular bonds.
4. Hydrogen bonds are also some what weak, having energies ranging from 7 to 40kJ/mol.
5. Hydrogen bonding has considerable importance in stabilizing structures by intra molecular bond formation.
6. Classical examples of such bonding occur in the protein α-helix and in the base pairs of DNA.
7. Surprisingly, hydrogen bonds are probably less important in intermolecular bonding between two structures (i.e., the drug and its receptor) in aqueous solution because the polar groups of such structures form hydrogen bonds with the solvating water molecules.
8. There is no advantage in exchanging hydrogen bonding with water molecules for hydrogen bonding with another molecule unless additional, stronger bonding brings the two molecules into sufficient proximity.

Q11. Discuss the binding role of $-NH_2$ group Quaternary ammonium salts and double bond drug binding receptor interactions.

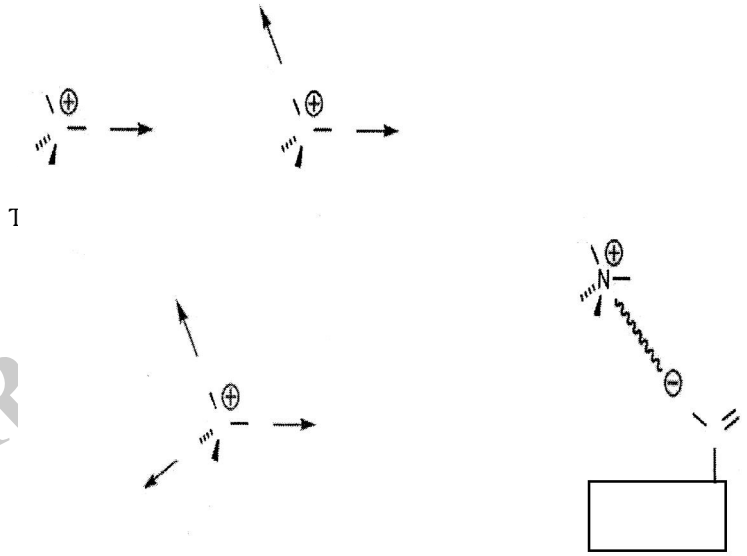
Ans : **(Imp.)**

NH_2 group, quaternary ammonium salts:

1. Amine and its derivatives very important functional groups in medicinal chemistry and are present in many drugs.
2. They may be involved in H-bonding either as an HBA or an HBD.
3. The N-atom has one lone pair of electrons and can act as an HBA for one H-bond.
4. Primary and secondary amines have N–H groups and can acts as HBDs.
5. Aromatic and heteroaromatic amines act only as HBDs, because the lone pair interacts with the aromatic or heteroaromatic ring.

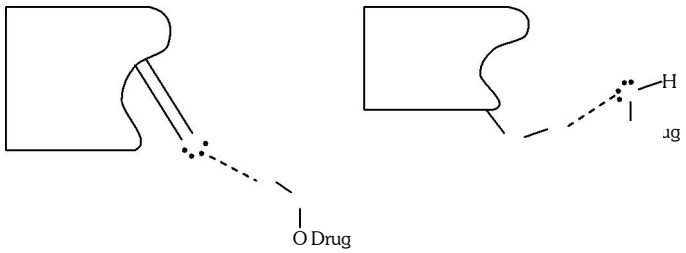


6. In many cases, the amine may be protonated when it interacts with its target binding site, which means that it is ionized and cannot act as an HBA.
7. However, it can still act as an HBD and will form a stronger H-bond than if it were not ionised.
8. Alternatively, a strong ionic interaction may take place with a carboxylate ion in the binding site (right-hand graphic).



Binding role of OH Group in Receptor

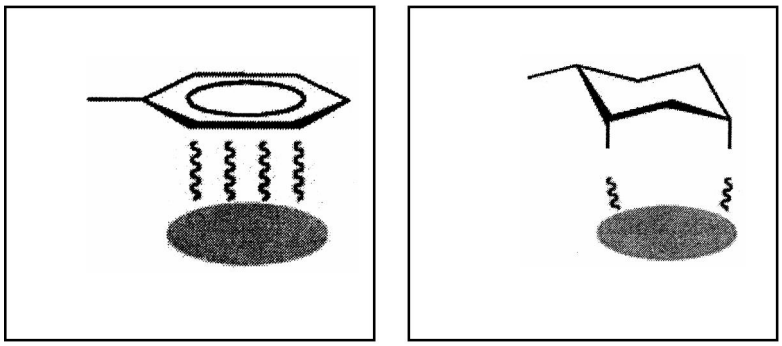
Alcohol and phenol hydroxyls are common in drugs and are often involved in hydrogen bonding oxygen as a H bond acceptor (HBA) and the hydrogen as hydrogen as hydrogen bond donor (HBD).



Double bond and Aromatic Rings Bonding Interactions

Alkenes are also planar and hydrophobic so they too can interact with hydrophobic regions of the binding site through vander waals and hydrophobic interactions. They are often reduced to saturated systems in order to investigate their binding role.

Aromatic rings are planar, hydrophobic structures, commonly involved in vander waals and hydrophobic interactions with flat hydrophobic regions of the binding site.



Q12. Describe the structure activity relationships of sulfonomides.

Ans : **(Imp.)**

1. Structure-Activity Relationships (SAR) are the traditional practices of medicinal chemistry which try to modify the effect or the potency (i.e. activity) of bioactive chemical cmpounds by modifying their chemical structure.
2. Medicinal chemists use the techniques of chemical synthesis to insert new chemical groups into the biomedical compound and test the modifications for their biological effects. This enables the identification the determination of the chemical groups responsible for evoking a target biological effect in the organism.
3. This method was later refined to build mathematical relationships between a chemical structure and its biological activity, known as Quantitative Structure-Activity Relationships (QSAR).
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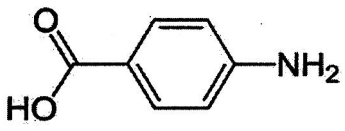
   Structure-activity relationships (SAR) of Sulfonilamide drug :



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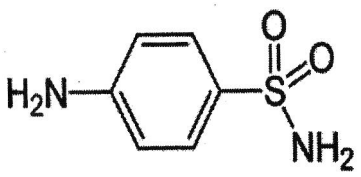
6. The p-amino benzene sulphonamide is known as sulphanilamide, it was first synthesized by Gelmo in 1908.

7. Sulphanilamide is a sulfonamide antibiotic. The sulphonamides are synthetic bacteriostatic antibiotics with a wide spectrum against most gram positive and many gram-negative organisms.
8. However, many strains of an individual species may be resistant. Sulphonamides inhibit multiplication of bacteria by acting as competitive inhibitors of p-amino benzoic acid in the folic acid metabolism cycle.
9. Bacterial sensitivity is the same for the various sulfonamides, and resistance to one sulphonamide indicates resistance to all. Most sulfonamides are readily absorbed orally. However, parenteral administration is difficult, since the soluble sulfonamide salts are highly alkaline and irritating to the tissues.



SAR Studies

1. The amino and sufonil groups on the benzene ring should be para position to each other for the drug to slow down the activity.
2. The amino group should be un-substituted for the better activity.
3. Replacement of benzene ring by other aromatic ring systems decrease the activity.
4. Exchange of SO_2NH_2 group with aromatic group retains the activity.
5. Mono Substitution at N of SO_2NH_2 group increases the activity.
6. Di Substitution at N of SO_2NH_2 group decrease the activity.

Short Question and Answers

1. What are enzymes?

Ans :

Enzymes can be defined as soluble, collodial, organic catalysts which are produced by living cells but are capable of acting independently of the cells. Most enzymes are protein in nature and exhibit all properties of the proteins. They are water soluble; precipitated by the usual protein precipitating reagents like alcohol, ammonium sulfate and alkaloidal reagents; they are non-dialyzable, amphoteric, have isoelectric points and have a nitrogen content of about 16%. Extreme alterations of pH and high temperatures denature the enzyme protein and thus make it inactive.

2. Mention the enzyme specificity.

Ans :

Enzyme Specificity

Specificity is a characteristic property of the active site.

i) Stereospecificity or optical specificity

Stereoisomers are the compounds which have the same molecular formula differ in their structural configuration.

The enzymes act only on one isomer

Ex: L-amino acid. Oxidase and D-amionacid oxidase act on L- and D-aminoacids. Hexokinase on D-glucose amylase acts on α - glycosidic linkages, cellulose cleaves β - glycosidic bond.

Stereospecificity is explained by considering three distinct region of substrate molecule specifically binding with three complementary regions on the surface of the enzym. The ezymes belonging to isomerases do not exhibit stereospecificity.

ii) Reaction specificity

The same substrate can undergo different types of reaction each catalysed by a seperate enzyme. and this is referred to as reaction specificity. An Amino acid can undergo transamination.

iii) Substrate specificity

The substarte specificity varies from enzyme to enzyme. It may be either absolute, relative or broad.

Absolute substrate specificity certain enzymes act only on one substrate eg: Glucokinase acts on glucose to give glucose-6-phosphate, urease cleaves urea to ammonia and carbondioxide.

3. Write about Irreversible enzyme inhibitors.

Ans :

Irreversible or non-competitive inhibition:

Many enzymes like papain, urease and succinic dehydrogenase require for their activity the presence of free –SH groups in their molecules. The addition of glutathione, cysteine, H_2S and traces of HCN activate such enzymes by preventing oxidation of the –SH group. Compounds like iodoacetate and P-chloromercuribenzoate (PCMB) combine with –SH groups and thus inactivate the enzymes. Heavy metals like Ag^+, Hg^{++} also combine irreversibly with the –SH groups and inactivate enzymes. Some enzymes which require metallic ions for their activity are inhibited by chelating agents like ethylenediamine tetraacetate (EDTA).

Di-isopropylfluorophosphate (DFP) inhibits acetylcholinesterase by combing with a serine residue at the active site of the enzyme. Transmission of nerve impulses is blocked leading to paralysis.

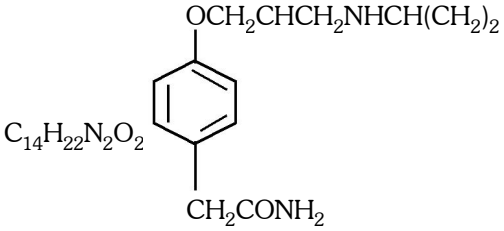
This type of inhibition is irreversible and will make the active site of the enzyme ineffective. Addition of any amount of the substrate does not restore activity.

4. Define Antagonists.

Ans :

A drug molecule may bind to the receptor site without causing aresponse. If, by binding in this way, the drug prevents further ligands binding (byblocking the site or causing a conformational change) then the drug molecule is known as an antagonist.

E.g. Mechanism action of an Antagonist drug Atenolol



These are β adrenergic antagonist and acts as antihypertensive agent use to treat arrhythmia (abnormal heart beat). When these drugs bind to β adrenergic causes dilation of blood vessels relaxation of heart muscle causes the decreased cardiac output, slow down the heartbeat, reduces the force of the attack in heart.

Longer usage may cause brancheo contraction causes asthma.

Atenolol is the cardio selective, β receptor blocker antihypertensive agent and longer duration of action available as tablet forms 5 to 25 mg.

5. Define agonists and mention the types of agonists.

Ans :

An agonist is a drug that interacts with a receptor and produces an observable biological effect similar to that of endogenous substance (adrenaline).

Adrenaline is an endogenous substance which binds to the β adrenergic receptor of bronchioles in lungs leading to the brancheo dilation.

If there is less adrenaline in the body it leads to symptoms of asthma.

Salbutamol is an β adrenergic agonist drug has structural similarities with the adrenaline, binds to the receptor causing brancheo dilation similar to that produced by adrenaline.

It is used to treat asthma and branchiole asthma, lung diseases.

It selectively binds adrenergic receptors; the natural neuro transmitter noradrenaline sufficiently releases bronchiole expansion and contraction happens smoothly but when noradrenaline secretion was reduced bronchioles were contracted.

When, an agonist drug inhaled by the living system which the role which carries similar to norarenaline and effective function of lugs i.e expansion and contraction takes place.

Partial agonists are able to activate a receptor but cannot produce a maximal signalling effect equivalent to that of a full agonist even when all available receptors are occupied. When mixed with full agonist, partial agonists block receptor sites that could potentially be occupied by the full agonist, which reduced the overall response (i.e. they seem to antagonize the effect of the full agonist).

Partial agonists have some advantaged as therapeutic agents. Although they are unable to achieve the same maximum effect as the full agonist, they are less likely to produce receptor-mediated adverse effects at the top of their dose-response curve (e.g. the partial opioid receptor agonist buprenorphine does not cause as much respiratory depression as morphine when it is used as an analgesic).

Inverse agonists produce the opposite effect to the full againost when they bind to a receptor. For inverse agonists to be identified, the revelant endogenous receptor must show some degree of coupling to a biological response even in the absence of ligand binding (i.e. constitutive activity). Many receptors posses constitutive activity.

6. Write about covalent bonding interactions in drug receptor complex.

Ans :

Covalent Bonding Interactions

1. Covalent bonds are lessimportant in drug-receptor binding than non-covalent interactions.
2. It is generally not desirable to have a drug covalently linked to its receptor, since such an interaction would persist for a long period of time.
3. Such prolonged interactions tend to lead to difficulties with lengthy drug half-lives and potentially to toxicity problems.
4. Accordingly, the only receptors to which covalent binding is desirable are those that belong to exogenous.
5. Drugs with short duration of action generally have weaker bonds, log duration or irreversible drug receptor interactions may have stronger bonds such as covalent/

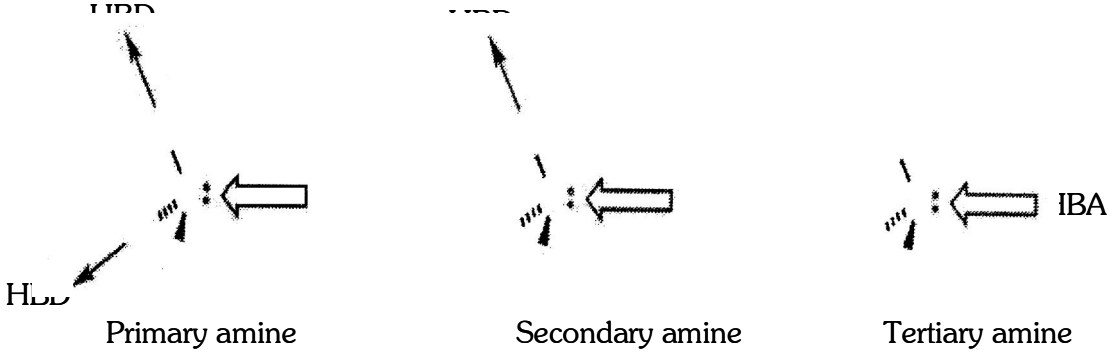
   e.g., Pencilline

7. Discuss the binding role of $-NH_2$ group, Quaternary ammonium salts in drug binding recptor interactions.

Ans :

NH_2 group, quaternary ammonium salts:

1. Amine and its derivatives very important functional groups in medicinal chemistry and are present in many drugs.
2. They may be involved in H-bonding either as an HBA or an HBD.
3. The N-atom has one lone pair of electrons and can act as an HBA for one H-bond.
4. Primary and secondary amines have N–H groups and can acts as HBDs.
5. Aromatic and heteroaromatic amines act only as HBDs, because the lone pair interacts with the aromatic or heteroaromatic ring.



Primary amine Secondary amine Tertiary amine

8. Write any three factos effecting enzyme action.

Ans :

Physical Factors altering enzyme activity

i) Concentration of the enzyme:

Within reasonable limits, the initial rate of an enzyme reaction is directly proportional to the concentration of the enzyme. In course of time, due to accumulation of products of the reaction and the tendency for the reaction in the reverse direction, the rate of enzyme reaction diminishes. shows the reaction-enzyme relations immediately on addition of the enzyme.

ii) Concentration of the products:

Accumulation of products of reaction causes a lowering of the enzyme activity. This is prevented in nature by prompt removal of the products from the site of formation, e.g.absorption of the products of digestion from gastrointestinal tract into the blood stream.

iii) pH:

Some enzymes act best in an alkaline medium; others in an acid medium. For every enzyme there is a pH where it acts at its best and this is its optimal pH. The optimum pH for pepsin is around 2.0 while that of trypsin varies from pH 8.0 to 9.0. It is probable that pepsin attacks the substrate molecules best if they carry a positive charge while trypsin attacks the negatively charged substrate molecules. For most biological enzymes the optimum pH is around 7.4.

9. Write about reversible competitive inhibition.

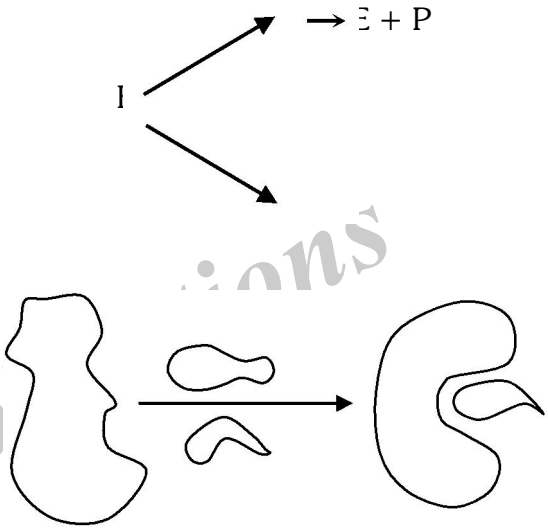
Ans :

Reversible Inhibition

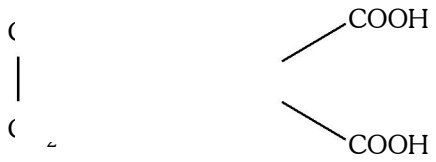
The inhibitor binds noncovalently with enzyme and the enzyme inhibition can be reversed if the inhibitor is removed. The reversible inhibitor is further sub divided into

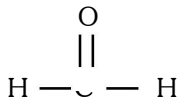
Competitive inhibition

The inhibitor which closely resembles the real substrate is regraded as substrate analogue. The inhibitor competes with substrate and binds with the active site of the enzyme but does not undergo any catalysis. As long as the competitive inhibitor holds the active site the enzyme is not available for the substrate to bind. During the reaction ES & EI complexes are formed



The inhibition could be overcome by a high substrate conc. The k_m value Tses V_{max} remains unchanged.



Methanol is toxic to the body when it is converted to  by the enzyme alcohol dehydrogensae (ADH) Ethanol can compete with methanol for ADH. Ethanol can be used in the treatment methanol poisoning.

10. Describe the structure activity relationships of sulfonomides.

Ans :

1. Structure-Activity Relationships (SAR) are the traditional practices of medicinal chemistry which try to modify the effect or the potency (i.e. activity) of bioactive chemical cmpounds by modifying their chemical structure.
2. Medicinal chemists use the techniques of chemical synthesis to insert new chemical groups into the biomedical compound and test the modifications for their biological effects. This enables the identification the determination of the chemical groups responsible for evoking a target biological effect in the organism.
3. This method was later refined to build mathematical relationships between a chemical structure and its biological activity, known as Quantitative Structure-Activity Relationships (QSAR).
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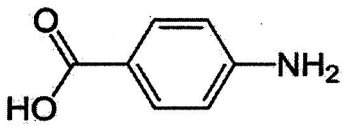

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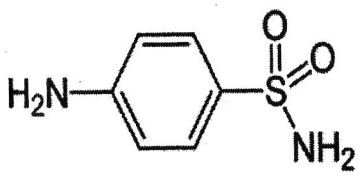

SAR Studies

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Choose the Correct Answers

1. _____ Enzyme cleares urea to Ammonia and Co_2 [b]
   (a) Pharmacodynamic agent (b) Receptor
   (c) Pharmacaphore (d) Metabolite
2. Atenolol _____ type of drug. [c]
   (a) Antipyretic (b) Antileprosy
   (c) Antihypersensitive (d) Antidiabetic
3. Salbutamol _____ type of drug. [b]
   (a) α (b) β
   (c) γ (d) All
4. Sulfonamides are inhibitors of _____ in fabeacid metabolism. [a]
   (a) PABA (b) Fats
   (c) Carbohydrates (d) Proteing Benzoicacid
5. _____ oxidise the enzymes for inactive. [c]
   (a) Acids (b) Bases
   (c) Peroxides (d) Neutral componds
6. The coenzyme is _____ [c]
   (a) Often a metal (b) Always a protein
   (c) Vitamin (d) An inorganic compound
7. Blocking of enzyme action by blocking its active site is called as _____ [c]
   (a) Allosteric inhibition (b) Feedback inhibition
   (c) Competitive inhibition (d) Non-competitive inhibition
8. Enzymes are made up of [b]
   (a) Fats (b) Proteins
   (c) Nucleic acids (d) Vitamins
9. Enzymes are polymers of [b]
   (a) Hexose sugar (b) Aminoacids
   (c) fattyacids (d) Inorganic phosphate
10. In human body optimum temperature for enzymatic activity is [a]
    (a) 37°C (b) 25°C
    (c) 20°C (d) 15°C

Fill in the Blanks

1. Enzymes are _____.
2. Enzymes are inactive at _____.
3. Biological enzymes the optimum pH is _____.
4. A drug which ineracts with a receptor and produces an observable biological effect is known as _____.
5. A drug molecule bind to the receptor site without causing a response is known as _____.
6. Atenolol is _____ drug.
7. Sulfonamides are _____ type of drugs.
8. In drug binding receptor interactions $-NH_2$ gp binded by _____.
9. Salbutamol is an example of _____.
10. Covalent bonding interactions leads to _____.

ANSWERS

1. Catalyts
2. O°C
3. 7.4
4. Agonist
5. Antagonist
6. Antagonist
7. Antibacterial
8. Hydrogen binding
9. Agonist
10. Long duration of action.

UNIT - III

(Medicinal Chemistry)

Synthesis and Therapeutic Activity of Drugs

S6-E-A-III: Introduction, synthesis and therapeutic activity of Chemotherapeutics: Sulphanilamide, dapsone, Penciliin-G (semi synthesis), Chloroquin, Isoniazid, Cisplatin and AZT.

Drugs to treat metabolic disorders: Anti diabetic - Tolbutamide; Antiinflammatory - Ibuprofen; Cardiovascular- Glyceryl trinitrate; Antipyretic (paracetamol, aspirin) and Antacid- Omeprazole.

Drugs acting on nervous system: Ancslhetics-definition, Classification-local and general. Volatile- Nitrous oxide, chloroform uses and disadvantages. Local anaesthetics - benzocaine.

Synthesis and Therapeutic Activity of Drugs

Q1. Discuss the synthesis of sulphanilamide and its therapeutic activity.

Ans : **(Imp.)**

Sulphanilamide

Sulphonamides are useful as drugs are called sulpha drugs. Sulphanilamide is an example of sulpha drugs. Sulphanilamide is a bactereostatic drug, that is, one which inhibits the growth of bacteria. Bacteria synthesize folic acid (vitamin B_9) which is necessary for their growth. The key compound for the synthesis of folic acid is p-amino benzoic acid (PABA). The drug, sulphanilamide is a structural analog of PABA. Bacteria cannot discriminate between the two and hence uses sulphanilamide instead of PABA. As a result, pseudo-folic acid is synthesized thereby inhibiting further growth of bacteria.

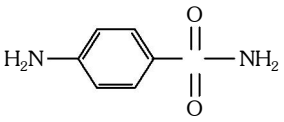


Fig. : Sulphanilamide (4-Aminobenzenesulfonamide)

Synthesis of Sulphanilamide

Sulphonamides are amides of sulphonic acid. Synthesis of sulphanilamide can be achieved in two different methods - method one is starting from aniline and the other method is starting from chlorobenzene.

Method-I (from aniline)

The acetylation of aniline gives acetanilide which, on chlorosulphonation, yields 4-methylcarboxamideo-1-benzenesulphonyl chloride. This drug intermediate is subjected to ammonolysis followed by deacetylation (through hydrolysis) to give sulphanilamide.

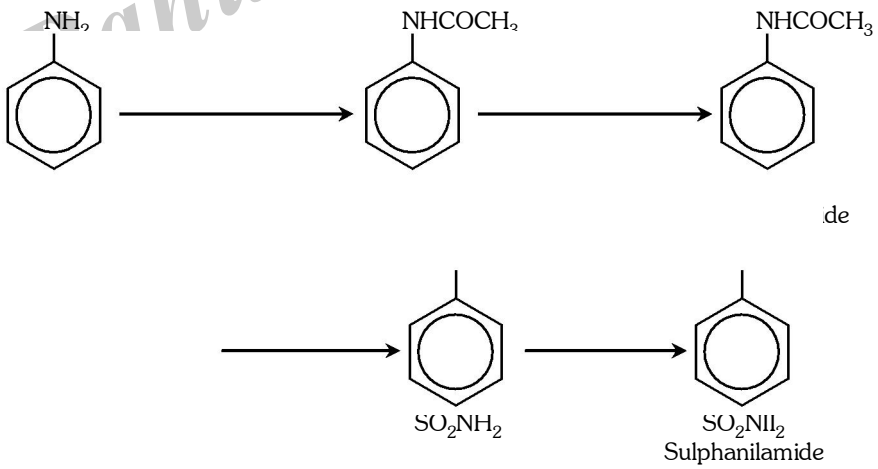


Fig. : Syntheis of Sulphanilamid (Method-I)

Method-II (from chlorobenzene)

The chlorosulphonation of chlorobenzene gives intermediate 4-chlorobenzenesulphonyl chloride. This intermediate is then subjected to ammonolysis, reaction with ammonia, to yield sulphanilamide.

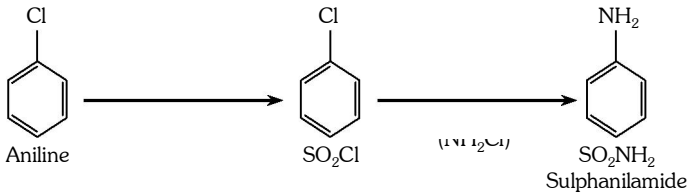


Fig.: A Synthesis of Sulphanilamide (Method-II)

Q2. Draw the structure of Dapsone and its preparation and therapeutic activity.

Ans : **(Imp.)**

Dapsone:

Dapsone is used to treat leprosy. Lesions of the skin, loss of sensitivity to pain, and superficial nerves are the three main signs of leprosy, a disease caused by the mycobacteria Mycobacterium leprae. This disease is extremely infectious. Children and men are more susceptible to it then women. The incubation period can last several years, which makes early detection of leprosy difficult. Chemotherapy of leprosy consisted of taking dapsone, which gave good clinical results. However, because of the primary and secondary resistance that originated from prolonged use, it is now necessary to use a certain combination of drugs. Currently, dapsone is used along with rifampin and clofazimine. Ethionamide is also prescribed.

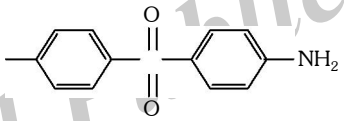


Fig.: Dapsone

Dapsone, which was first proposed in 1941, possesses both bactericidal as well as bacteriostatic acitivity with respect to Mycobacterium leprae and Mycobacterium tuberculosis. It is used to treat patients with herpetiform dermatitis. It is believed that the mechanism of its action consists of competitive inhibition of the enzyme dihydroprotease synthetase, which blocks synthesis of folic acid in microorganisms, allowing it to also be viewed as an analog of p-aminobenzoic acid. Synonyms of this drug are avosulfon, croysulfon.

Synthesis of Dapsone

Dapsone, 4,4-diaminodiphenylsulfone, is synthesized either from 4-chloronitrobenzene (Method - I) or from the sodium salt of 4-acetamidobenzenesulfonic acid (Method - II).

Method-I

Reacting 4-chloronitrobenzene with sodium sulfide gives 4,4-dinitrodiphenylthioether, and oxidation of the sulfur atom in this compound using potassium dichromate in sulfuric acid gives 4,4-dinitrodiphenylsulfone. Reduction of the nitro group in the resulting compound using tin dichloride in hydrochloric acid makes the desired dapsone. It has also been suggested to reduce the nitro group to an amino group, protect it with an acetyl protection, oxidize the sulfur atom to a sulfone using potassium dichromate, and then remove the acetyl protective group by hydrolysis.

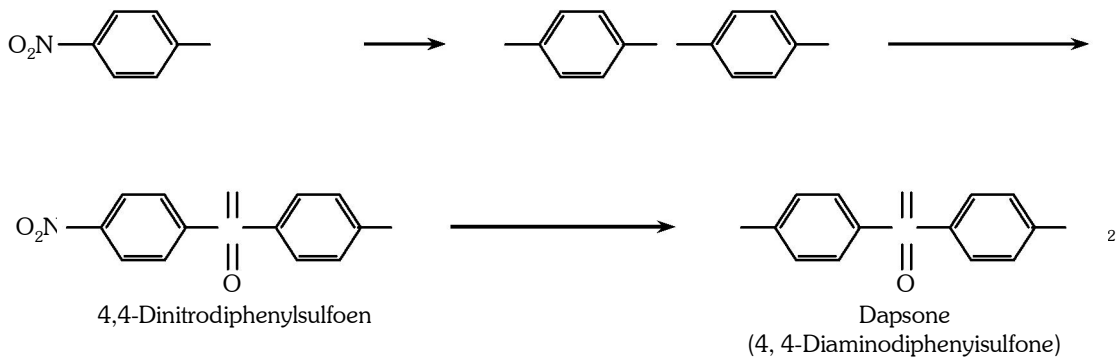


Fig: Synthesis of dapsone (Method-I)

Method-II

Another way of the synthesis of dapsone begins with sodium salt of 4-acetamidobenzenesulfonic acid, which is reacted with 4-chloronitrobenzene at high temperatures to give 4-acetamido-4-nitrodiphenylsulfone. Reducing the niro group in this compound with tin dichloride in hydrochloric acid along with the simultaneous hydrolysis of the acetyl group under the reaction conditions gives the desired dapsone.

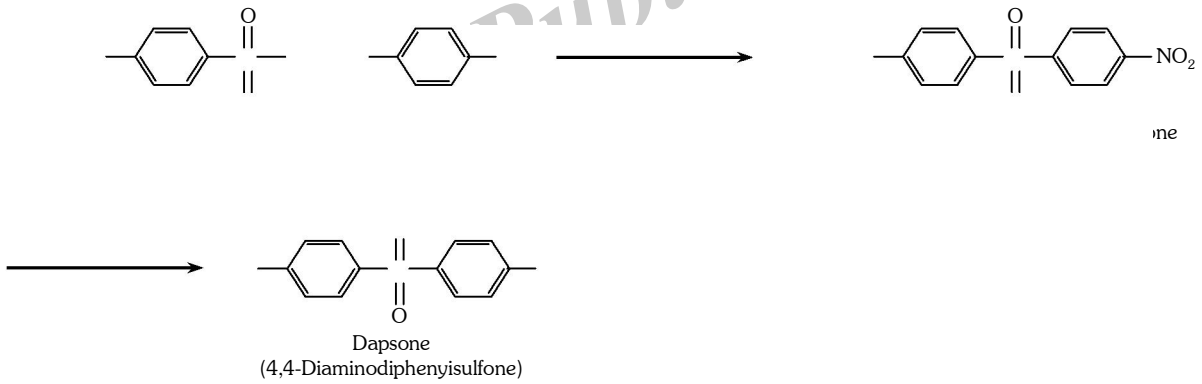


Fig: Synthesis of dapsone (Method-II)

Q3. Explain the semisynthesis of pencillin–G.

Ans : **(Imp.)**

Production and isolation of pencillin

Pencillin is manufactured by aerobic fermentation. The source of organism for this process was, initially Pencillin notatum. But now Pencillium chrysogenum is used because it produces higher yield of pencillin. Corn steep liquor is used as a fermentation medium and it consists of various ingredients as shown in Table.

Table: Ingredients for Pencillin Synthesis by Fermentation

Types of Ingredients	Specific Ingredients (%)
Main carbohydrate	Lactose, 3.0 - 4.0
Other carbohydrates	Glucose, 0 - 0.5 and Polysaccharides
Organic acids	Acetic, ~ 0.05, Lactic, ~ 0.5
Special precursors	Phenylethylamine
Main N source	Amines, amino acids, peptides
Other N source	Ammonia

Production and isolation of pencillin G: Step-by-step description of various stages.

1. Spores of Pencillin chrysogenum are used to inoculate the medium in a flask.
2. Shaker flask. The flask is incubated for 4-days on a shaker at 25^0C.
3. Transfer vessel. The contents of the flask is transferred into a medium and incubated at 25^0C.
4. Seed tank (reactor). The contents of the transfer vessel are passed into a stainless steel tank and incubated for 3 days.
5. Fermentation tank. The contents of the reactor is transformed into a medium in a fermentor and incubated for 5-6 days to produce pencillin.
6. Rotary filter. The contents of the fermentation vessel is filtered.
7. Extractors. The filtrate is passed into a series of extractors, wherein pencillin is extracted into amyl alcohol.
8. Vacuum still. The crystallization of pencillin takes place here.
9. Pencillin is extracted into aq.phosphate buffer from amyl acetate and filtered and crystallizes (from butanol-water mixture and converted into potassium salt or procaine salt).
10. Vacuum drier Pencillin G is freed from solvent impurities.

Pencillin

The term 'penicillins' represent a group of comounds with closely related structures. One of the most important discoveries in the 20th century was the discovery of penicillin, which was discovered in 1928 by Alexander Flemming, an English bacteriologist. The two natural penicillins obtained from culture filtrates of penicillium notatum or the closely related species P chrysogenum are penicillin G and the more acid-resistant penicillin V. They are active only against Gram-positive bacteria (which have a thick layer of peptidoglycan in the wall) and not against Gram-negative species, including many serious pathogens like Mycobacterium tuberculosis (the cause of tuberculosis).

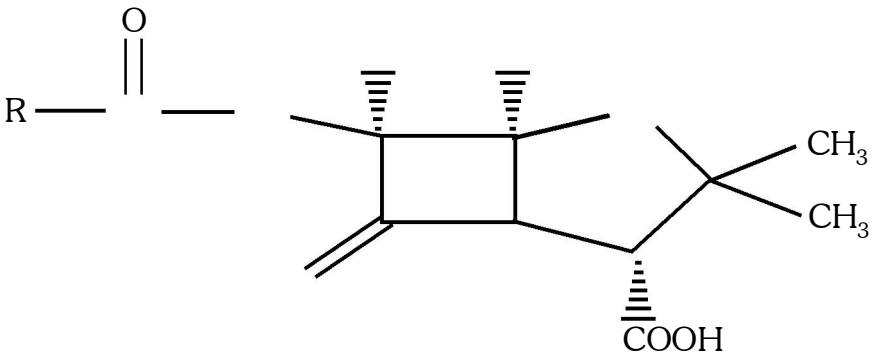


Fig.: Penicillins

Pencillin G(Benzyl Penicillin) : $R - C_6H_5CH_2$

Pencillin V(Phenoxypenicillin): $R–C_6H_5CH_2O$

Pencillin-G or benzyl penicillin

The first penicillin that was widely used in Penicillin G or benzyl penicillin. Penicillin G possesses many of the qualities of an "ideal" antibiotic. It is relatively non-toxic to the patient (or host) and it is effective against a wide variety of organisms including fungi. It is obtained from fermentations of Pencillium chrysogenum mold and is classified as a narrow spectrum drug effective against many gram positive, some gram negative organisms and some anarobes. Benzyl penicillin is available as benzyl penicillin sodium or benzyl pencillin potassium. Structurally, penicillin consists of a β-lactam ring fused onto a thiazolidine ring. Hence, this class of drugs is also called as β-lactam group of antibiotics.

Penicillin acts by preventing the synthesis of cell-walls by certain bacteria and causes their death. The cell-walls of bacterial are made up of mucoproteins (polymers of amino sugars and proteins). At the molecular level, penicillin inhibits an active enzyme of bacteria, peptidoglycan transpeptidase, which is responsible for the construction of the cell wall, in which the amino group of the enzyme opens up the β-lactam ring of penicillin making the enzyme inactive. Penicillin does not harm human cells. However, penicillin G and V have possible allergic reactions and other side effects in some people.

Currently, several semi-synthesis penicillins are being used as antibacterials. The fermentation of Penicillinium chrysogenum produces penicillamine. The chemical reaction of pencillamine with D-phenylglycine and p-hydroxy-D-phenylglycine, produces ampicillin and amoxicillin, respectively. Amoxicillin is the world's highest-selling antibiotic drug.

Q4. Write the synthesis and therapeutic activity of chloroquine.

Ans : **(Imp.)**

Synthesis of Chloroquine:

Chloroquine, 7-chloro-4-(4-diethylamino-1-methylbutylamino)-quinoline, is a quinolines derivative. It is made by reacting 4,7-dichloroquinoline with 4-diethylamino-1-methylbutylamine at 180^0C.

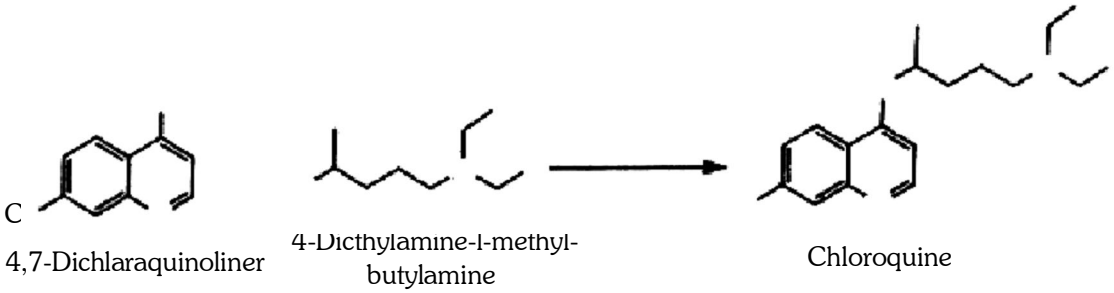


Fig.: Synthesis of chloroquine

The necessary 4, 7-dichloroquinoline is prepared in several ways from 3-chloroaniline. One of these ways consists of reacting 3-chloroaniline with ethoxymethylenmalonic ester to make (3-chloroanilino)-methylenemalonic ester, which then undergoes high-temperature heterocyclization to make the ethyl ester of 7-chloro-4-hydroxyquinolin-3-carboxylic acid. Hydrolyzing this with sodium hydroxide gives 7-chloro-4-hydroxyquinolin-3-decarboxylic acid, which when heated at 250 - 270^{0}C is decarboxylated, forming 7-chloro-4-hydroxyquinoline. Treating this with phosphorus oxychloride gives 4,7-dichloroquinoline one of the desired components necessary for synthesis of chloroquine, 4,7-dichloroquinoline.

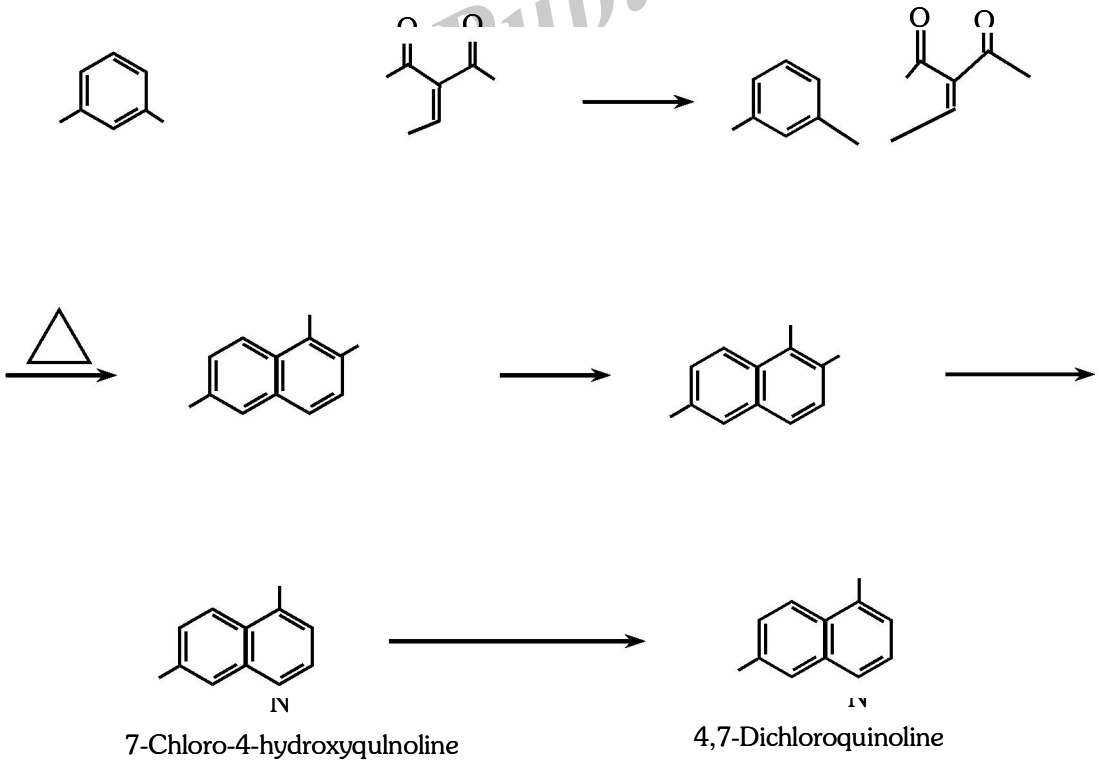


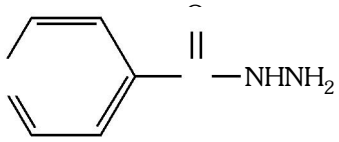
Fig.: Synthesis of 4,7-dichloroquinoline

Q5. Mention the synthesis of Isoniazid and its therapeutic activity.

Ans :

Isoniazid

Tuberculosis is an infection caused by the Mycobacterium tuberculosis, which most often affects the lungs, and which is characterized by symptoms such as acute inflammation, tissue necrosis, and frequently by the development of open sores. In a few cases, the pathogen penetrates into the lymph or blood and the infection can spread to other body tissues. The modern therapy for tuberculosis is very effective, although it can be long and difficult. The pathogen quickly develops resistance to therapy using a single drug. Morever, many strains also developed resistance to bi- and even multi-drug therapy, and therefore anti tuberculosis drugs, as a rule, are used in the form of a combination of two or three drugs.



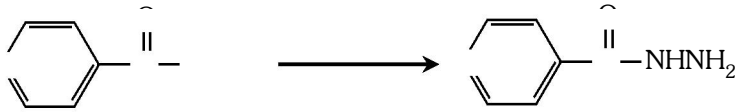
Drugs used for tuberculosis therapy are very different in terms of activity and toxicity, and they are divided into two groups. Drugs in the first group include those medicinal drugs with a high level of efficacy and relatively low toxicity. Isoniazid, ethambutol, pyrazinamide as well as the antibiotics rifampicin and streptomycin are included in this group.

Isoniazid, the hydrazide of isonicotinic acid was introduced into medical practice for treating tuberculosis in 1953. Isoniazid exhibits bactericidal action on Mycobacterium tuberculosis. It inhibits the synthesis of mycolic acid an important component of the cell membrane of mycobacteria. Mycolic acid is specific only to mycobacteria, and it is the cause of the selective toxicity of the drug with respect to these microorganisms.

Mutants that are resistant to isoniazid are rarely seen in nature, and in a spontaneously growing population of tuberculous bacillus there is approximately one mutant in every $10^5 – 10^6$ organisms. Large population of microorganismsof the order $10^9 – 10^{10}$ bacilli in the pulmonary cavities contain a significant number of resistant mutants. If only isoniazid is taken during treatment, an increased number of mutants will be observed and they will eventually become the dominant phenotype. The transformation from sensitive to non-sensitive microorganisms during treatment is called secondary or acquired resistance, which can originate over the course of a few weeks. Isoniazid is the most important drug for treating pulmonary and non-pulmonary forms of tuberculosis. It is active against both intercellular and extracellular organisms. In order to prevent secondary resistance, isoniazid should be used with other effective drugs (usually rifamin). Synonyms of this drug are tubazid, and razide, niazid, piridizin. The majority of patients using these drugs can be successfully healed.

Synthesis of Isoniazid

Isoniazid, isonicotinic acid hydrazide, is synthesized by reacting ethylester of isonicotinic acid with hydrazine.



Ethylester of Isonicotinic acid

Isoniazid (Isonicotinic acid hydrazide)

Figure: Synthesis of isoniazid

Q6. Explain the synthesis of Antic cancer cisplatin and its therapeutic activity.

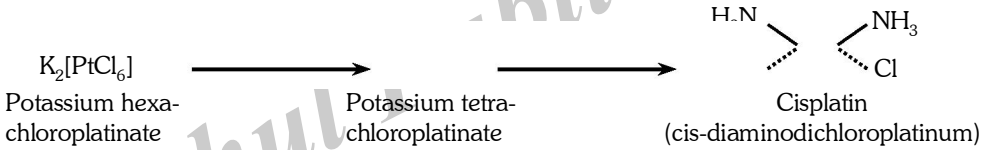
Ans :

Cisplatin

Cisplatin is a non-organic platinum-containing drug with alkylating properties. It causes cross-linking of DNA and RNA chains. Cisplatin, like other alkylating agents, bind primarily at N7 of two neighbouring deoxyguanylates to DNA, which inhibits its replication. It is only used intravenously. It is highly reactive with carcinomas of the testicles, ovaries, head, neck, spleen, lungs, and so on. Synonyms of this drug are platinol, platiblastin, platinex, neoplatin, and others.

Synthesis of Cisplatin

Cisplatin, cis-diaminodichloroplatinum, is made by reducing potassiumhexachloroplatinate by hydrazine to potassium tetrachloroplatinate, which reacts with ammonia to give cisplatin.



Potassium hexa-chloroplatinate

Potassium tetra-chloroplatinate

Cisplatin (cis-diaminodichloroplatinum)

Fig.: Synthesis of cisplatin

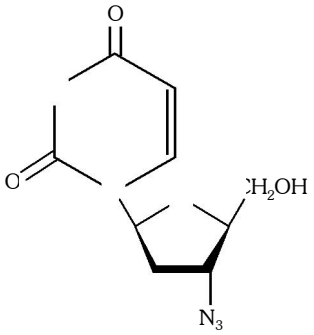
Q7. Write the synthesis and therapeutic activity of AZT.

Ans : **(Imp.)**

AZT (azidothymidine) or ZDV (Zidovudine)

AZT (azidothymidine) also known as Zidovudine (ZDV) is a thymidine analogue. It is 1-(3-azido-2,3-dideoxyb-D-erthyro-pentofuranosyl)-5-methylpyrimidine-2,4-(1H, 3H)-dione. Zidovudine is an antiretroviral drug that is clinically active againstt HIV-1 and is intended to treat HIV-infected patients. Zidovudine is an analog of thymidine that inhibits replication of the AIDS virus. It also turned into mono-, di-, and triphosphates by the same cellular enzymes that catalyze phosphorylation of thymidine and thymidine nucleosides. Zidovudine-triphosphate is then included in the terminal fragment of the growing chain of viral DNA by viral reverse transcriptase, thus causing the viral DNA chain to break apart in cells infected with the virus.

Zidovudine has been authorized for treating patients with AIDS. It significantly prolongs the life of the patient, although it has a number of toxic effects. Synonyms of this drug are azidothymidine and retrovir.



Synthesis of AZT (Zidovudine):

Zidovudine is 3-azido-3-deoxythymidine, is synthesized from 1-(2-deoxy-5-O-trityl-β-D-lyxosyl) thymine, which is treated with methane sulfonyl chloride in pyridine to make the corresponding mesylate. Replacing the mesyl group with an azide group using lithium azide in dimethylformamaide makes the product with inverted configuration at C3 of the furnaosyl ring. Heating this 80% acetic acid removes the trityl protection, giving zidovudine.

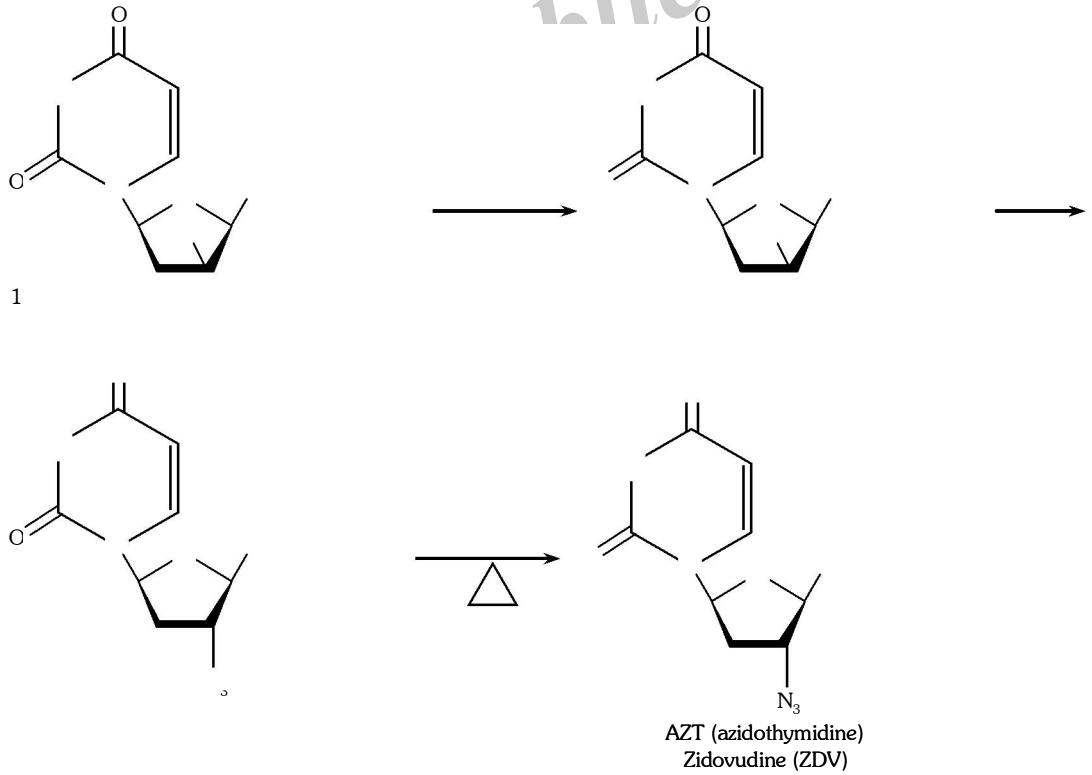


Fig.: Synthesis of AZT (azidothymidine) or Zidovudine (ZDV)

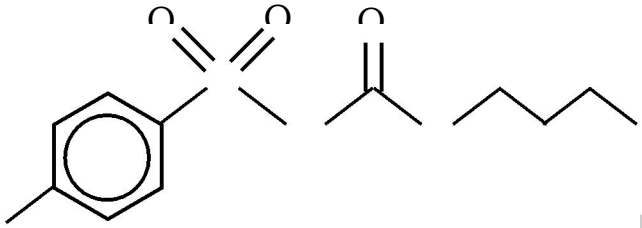
Drugs to treat metabolic disorders

Q8. Mention the drug to treat diabetis mellitus and give the therapeutic activity.

Ans : **(Imp.)**

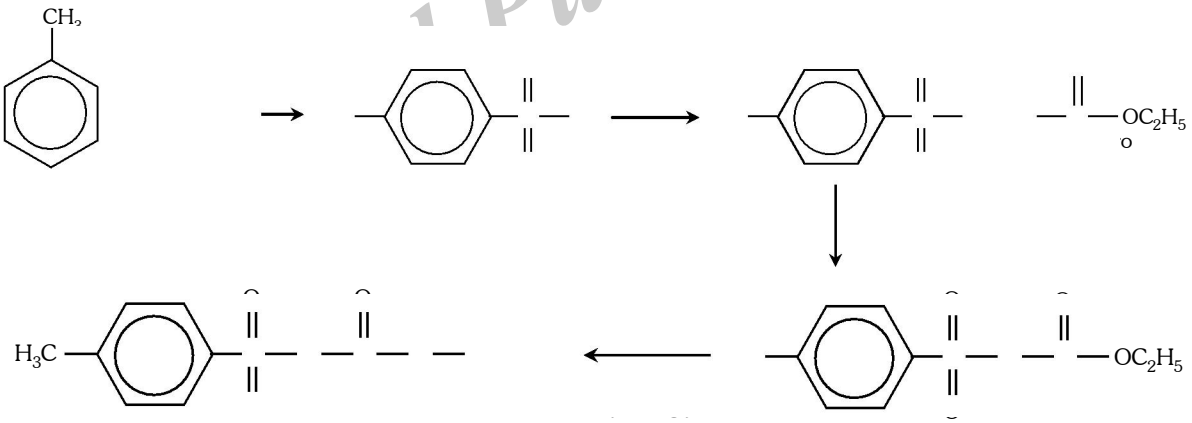
Tolbutamide

1. Tolbutamide is an orate antihyperglycemic agent used for the treatment of non insulin dependent diabeted mellitus (NIDDM).
2. It belongs to sulfoxylurea class of insulin secretagogues which act by stimulating β cells of the pancreas to release insulin.



3. Tolbutamide lowers blood sugar by stimulating the pancreas to secrete insulin and helping the body use insulin efficiently.

Synthesis



Mechanism of action

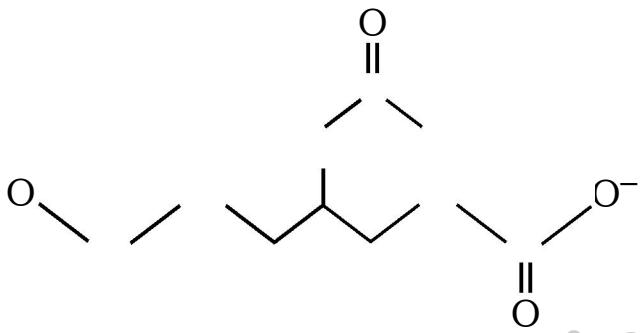
1. Sulfoxylurease lower blood glucose in pateints with NIDDM by directly stimulating the acute release of insulin from functioning beta cells of pancreatic islet tissue by an unknown process that involves a sulfoxylurea receptor on the beta cells.
2. Sulfoxylurease inhibit the ATP potassium channels on the beta cell membrane and potassium efflux which results in depolarization and calcium influx, calcium - calmodulin binding kinase activation and release of insulin - containing granules by exocytost an effect similar to that of glucose.

Q9. Give the cardiovascular drugs with examples.

Ans :

Glyceryltrinitrate

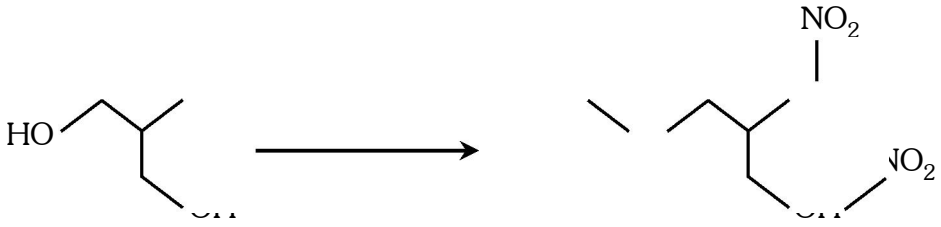
1. Nitroglycerin also known as glycerylnitrate is a medication used for heart failure, high blood pressure and to treat and prevent chest pain from not enough blood flow to the heart or due to cocaine.
2. It used as chest pain from a heart attack.



Nitroglycerin an organic nitrate is available in many forms as a vasodilator.

Mechanism of action

- Nitroglycerin is converted to nitric oxide (NO) an active intermediate compound which activates the enzyme.
- This stimulates the synthesis of cyclic guanosino 3', s' - monophosphate (CGMP) which then activates a series of protein kinase - dependent phosphorylation of the myosin light chain of the smooth muscle fiber.
- The subsequent release of calcium ions result in the relaxation of the smooth muscle cells and vasodilation.



Q10. Explain Paracetamol, aspririn synthesis and therapeutic activity.

Ans : **(Imp.)**

Paracetamol (Acetaminophen) : Antipyretic and Analgesic

Paracetamol is N-(4-hydroxyphenyl)-ethanamide (4-hydroxyacetanilide). The synthetic methods involve starting from phenol or 1-chloro-4-nitrobenzene, as shown in the synthetic plan (Fig. 3.4).

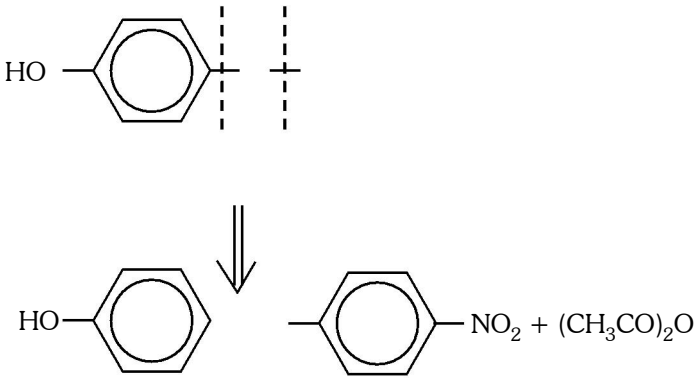
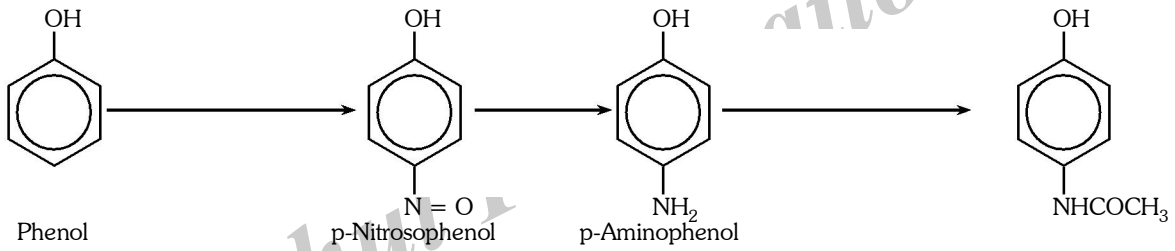


Fig.: The structure and synthetic plan of paracetamol

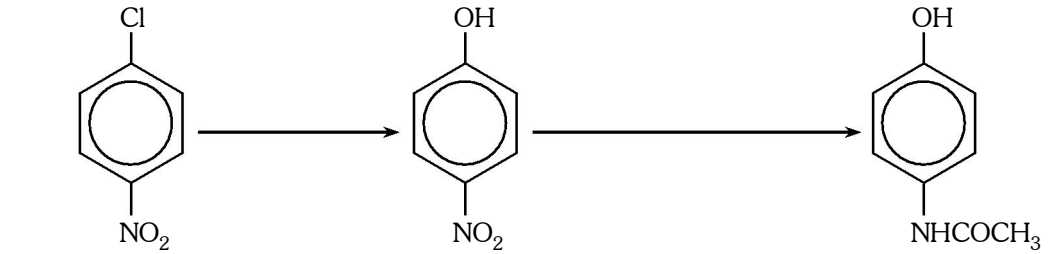
Synthesis

Method A (from phenol; Scheme 3.2a) Nitrosation of phenol gives 4-nitrosophenol which, on reduction, yields 4-aminophenol as a drug intermediate. This compound, on selective acetylation (acetylation of the amino group but not the hydroxy group), results in paracetamol.



Scheme 3.2a Synthesis of paracetamol starting from phenol.

Method B (from 1-chloro-4-nitrobenzene; Scheme 3.2b) The first step involves treatment of 1-chloro-4-nitrobenzene with aq.NaOH to yeild 4-nitrophenol. This reaction is an example of aromatic nucleophilic substitutin (S_NAr). In the second step, the nitro group of 4-nitrophenol is reduced to an amino group using H_2 in the presence of Pd-C as a catalyst, and the amino group is converted to acetamido group in presence of acetic anhydride. Both reduction and acetyaltion take place in one step.

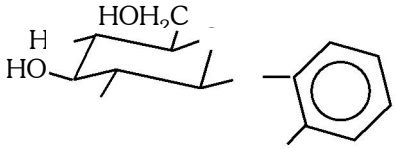


Synthesis of paracetamol starting from p-nitrochlorobenzene.

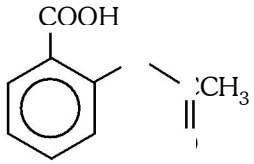
Therapeutic activity, Paracetamol is both an analgesic (pain-killing) and an antipyretic (fever-reducing) agent. It acts on the hypothalamus to reduce temperature - heat dissipation increases as a result of vasodilation and increased peripheral blood flow.

Aspirin (Acetylsalicylic acid): the first synthetic drug; synthesized in 1853 and introduced as a drug in 1899

The bark of the tree Salis alba ulgaris (willow) has been used from time immemorial to reduce fever. It contains "salicin" which is the glycoside of salicylic acid.



Salicin (glycoside of Salicylic acid)



Aspirin (Acetylsalicylic acid)

In the body, salicin is hydrolyzed into salicylic acid, which is responsible for its antipyretic and analgesic activity. The Bayer company synthesized several derivatives of salicylic acid and found that acetylsalicyclic acid (Aspirin) has good antipyretic, analgesic activity and also anti-inflammatory activity.

Synthesis of Aspirin is synthesized by acid-catalyzed acetylation of salicyclic acid, using acetic anhydride. (Salicyclic acid is, itself, synthesized from phenol using the Kolbe-Schmidt reaction).

Salicylic acid Aspirin

Synthesis of aspirin.

Therapeutic activity Aspirin is both analgesic and antipyretic (it falls at the mild end of the spectrum of analgesic activity). It is probably one of the most widely used drugs in the world for pain relief.

Aspirin, in the gastrointestinal tract, is hydrolyzed into salicylic acid and absorbed into the bloodstream. Salicylic acid is a metabolite of aspirin, and inhibits the enzymatic activity of prostaglandins synthase. This results in the controlled production of prostaglandins, which are responsible for the sensation of pain. The result is that the impulses responsible for pain are suppressed. Salicylic acid cannot be used as a drug directly. It is sour and causes severe intestinal bleeding, when taken orally; Aspirin does not cause such bleeding. This is the advantage of aspirin over salicylic acid as a drug; Aspirin is a prodrug.

Q11. Discuss the Antacid drugs. Give the therapeutic activity of omeprazole.

Ans :

Omeprazole : an antiulcer drug

Omeprazole contains two heterocylic moieties-benzimidazole and pyridine. The structure and synthetic plan of the drug are presented in Figure.

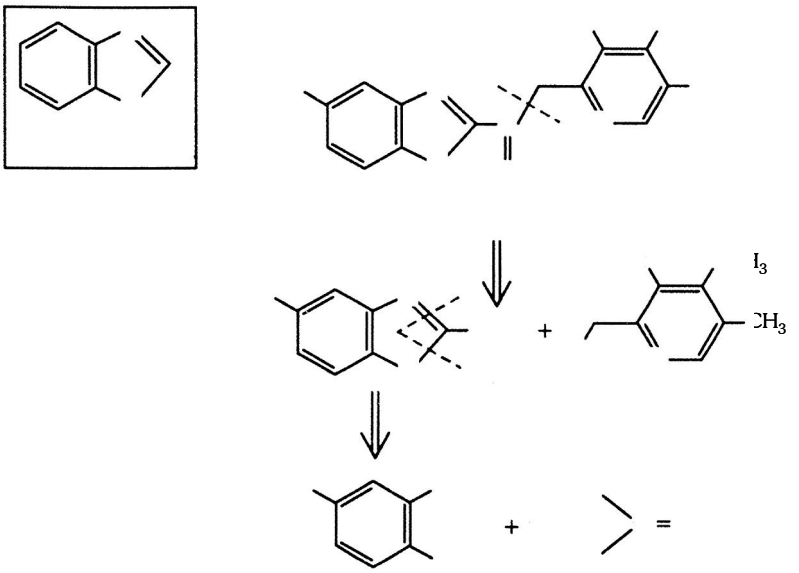
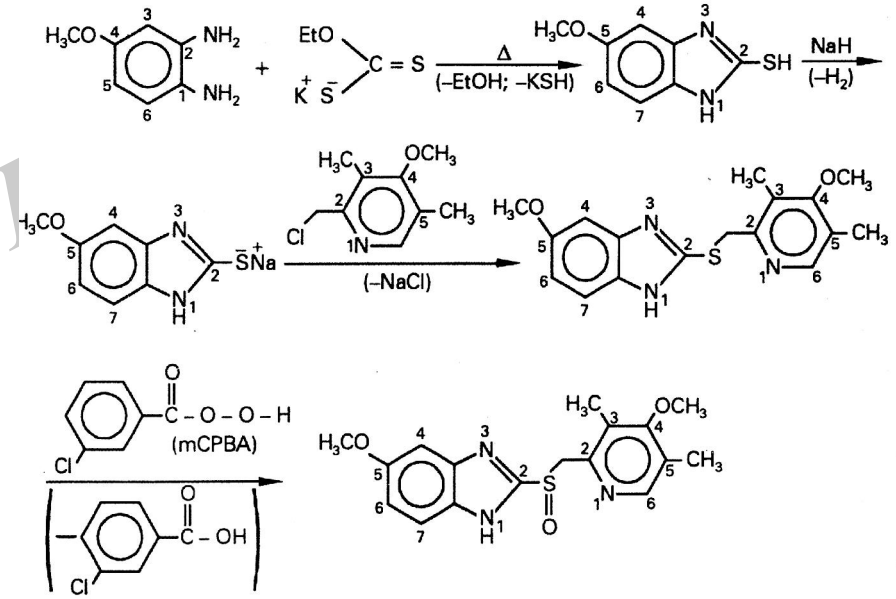


Fig.: The structure and synthetic plan of omeprazole.

Synthesis from the synthetic plan of omeprazole, three reactants are identified: i) 4-methoxybenzene-1, 2-diamine known as 4-methoxy-o-phenylene diamine, ii) potassium ethylxanthate, and iii) a substituted pyridine. The synthesis of omeprazole involves the construction of an imidazole ring of benzimidazole, followed by a reaction with substituted chloromethyl pyridine. Methoxy o-phenylene diamine undergoes



The synthesis of omeprazole.

cyclization with potassium ethylxanthate to yield 5-methoxybenzimadazol-2-thiol. (Potassium ethylxanthate is prepared by the action of sodium ethoxide with carbon disulphide). The thiol group of this intermediate is converted into sodium salt, on treatment with NaH, which undergoes S_N2 reaction with a pyridine derivative to yeild a thioether. The partial oxidation of sulphur, i.e, omeprazole.

Therapeutic uses The drug is useful for the treatment of ulcers (anti-ulcer drug). It acts directly on the stomach by inhibiting H^+, K^+ ATPase, which is responsible for acid secretion. It is an antisecretory agent.

Q12. Define Anesthetics.

Ans :

An anestheic is a drug used to induce anesthesia - in other words, to result in a temporary loss of sensation or awareness. Generally an ideal anesthetic should have the following characteristics. It should be: (i) non-inflammable, (ii) inexpensive, (iii) require uncomplicated equipment for administration, (iv) provide sufficient muscular relaxation, (v) have no effect on the myocardium or respiration at anesthetic doses, (vi) chemically and metabolically stable, (vii) sufficiently potent to permit adequate oxygen supply, and (viii) have a wide margin of safety.

Q13. Classify the local and general, volatile drugs uses and disadvantages.

Ans : **(Imp.)**

Classification of anesthetics

The drugs which effect the CNS may be divided into three broad categories. They are: (i) Non-selective CNS depressants, (ii) Non-selective CNS stimulants, and (iii) Selective modifiers of CNS. Anesthetics are one of the four sub-categories under Non-selective CNS depressants. Anesthetic may be further divided into two broad classes: general anesthetics, which cause a reversible loss of consciousness, and local anesthetics, which cause a reversible loss of sensation for a limited region of the body without necessarily affecting consciousness. A wide range of drugs with diverse chemical structures act as anesthetics. Historically, Horace wells (Hartford), a dentist, introduced nitrous oxide as an anesthetic in surgery in the year 1844, which was followed by use of ether by William Morton (Bostn), and the use of chloroform by James Simpson (Edinburgh).

Fig: Classification of CNS drugs

General Anesthetics

In surgical practice, the term general anesthesia (narcosis) presently refers to the condition of an organism with a reversible loss of consciousness at a controlled level of nervous system suppression. It includes the following components: analgesia (absence of pain), amnesia (absence of memory), suppression of reflexes such as bradycardia, laryngospasm, and loss of skeletal muscle tonicity. In modern medical practice, general anesthesia is a complex procedure involving pre-anesthetic assessment, administration of general anesthetic drugs, cardiorespiratory monitoring, analgesia, airway management, and fluid management. Accordingly, general anesthetics are drugs that provide relief of pain, weaken the reflex and muscle activity, and ultimately result in loss of consciousness. The ideal anesthetic must include the aforementioned characteristics, as well as to have a wide range of therapeutic index and to have no significant side effects. Drugs used in anesthesiology, block or suppress neurological impulses mediated by the central nervous system, and permit surgical, obstetric, and diagnostic procedures to be completed painlessly. General anesthetics are divided into two types - inhibition (halothane, enflurane, isoflurane, methoxyflurane, an nitrous oxide), and non-inhalation, intravenous (barbiturates, ketamine, and etomidate).

Volatile (Inhibition) Anesthetics

The object of inhalation anesthetics is to obtain a concentration (partial pressure) of the drug in the brain sufficient to reach the desired level of anesthesia. In order to do this, anesthetic molecules must pass through the lungs into the brain through various biological phases. Therefore, inhalation anesthetics must be soluble in blood and interstitial tissue.

The wide variation in structure, ranging from complex steroids to the inert mono atmoic gas xenon, led to several theories of anesthetic action. The mechanism by which inhalation anesthetics manifest their effect is not exactly known. Since they do not belong to one chemical class of compounds, the correlations between structure and activity are also not known. Inhalation anesthetics are nonspecific and therefore there are no specific antagonist. Interaction of inhalation anesthetics with cellular structures can only be described as vander waals interactions. There are a number of hypotheses that have been advanced to explain the action of inhalation anesthetics; however, none of them can adequately describe the entire spectrum of effects caused by inhalation anesthetics.

The action of general anesthetics can be explained as a blockage of ion channels, or as specific changes in mechanisms of the release of neurotransmitters. There of the proposed mechanisms are mentioned below.

1. Hydrate hypothesis

Anesthetic molecule can form hydrates with structured water, which can stop brain function in corresponding areas. However, the correlation between the ability to form hydrates and the activity of inhalation anesthetics is not known.

2. Ion channel hypothesis

Anesthetics block ion channels by interacting with cellular membranes and reducing the flow of Na^+ ions and increasing the flow of K^+ ions into the cell, which leads to the development of anesthesia.

3. Fluid membrane hypothesis

Anesthetics stabilize, or rather immobilize the cell membrane, hampering membrane fluidity, which produces changes in the ion channel action.

Selection of a specific anesthetic or combination of anesthetics is made depending on the type of medical intervention. For a long time, ether, chloroform, tricholoroethylene, ethylichloride or chloretane, and also cyclopropane were widely used as inhalation anesthetics. Today, the following anesthetics are used most regularly in medicine: Halothane, enflurane, isoflurane, methoxyflurance, and nitrous oxide. Researchers are also actively exploring the use of xenon as an anesthetic.

Q14. Discuss the Benzocaine local anaesthetic.

Ans :

Local Anesthetics

The anesthesia produced by local anesthetics is generally without loss of consciousness or the impairment of vital central functions. For this reason, local anesthetics play a key role clinically in dentistry and in other minor surgeries for temporary relief from pain. Local anesthetics are drugs that cause a state of loss of sensation by reversible blocking the nerve impulses that transmit the feeling of pain from the particular local area to the brain. Benzocaine (Topical), Lidocaine (Topical and Parenteral), Butacaine (Topical), Butamben (Topical), and Procaine (Parenteral) are among the some of the local anesthetics.

Benzocaine

Benzocaine is used in topical anesthesia on the skin and mucous membranes in the form of aerosols, or as creams for reduction of pain caused by itching, cuts, bites, etc. It begins to work 15-30 sec after application and lasts 12-15 min. It is also used under the names anestezin, dermoplast, and others.

Synthesis of Benzocaine

Benzocaine is the ethyl ester of 4-aminobenzoic aicd. The classic, optimal way of benzocaine synthesis is the reduction of the nitro group of the ethyl ester of 4-nitrobenzoic acid to benzocaine by hydrogen, which generates directly in the reaction medium by the reaction of iron filings with dilute acids.

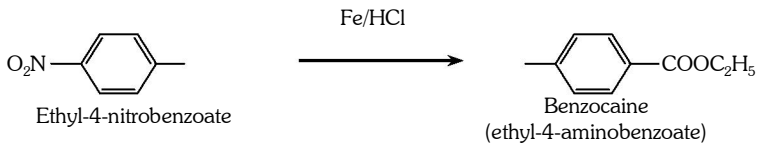


Fig: Synthesis of benzocaine or eythl-4-aminobenzoate

Q15. Write the Synthesis of Nitrous oxide.

Ans : **(Imp.)**

Nitrous Oxide

Nitrous oxide, which is also called laughing gas, is a weak anesthetic. It is usually used together with hypnotics, analgesics, and muscle relaxants. It is sometimes called an ideal anesthetic because of the

absence of any kind of suppressive influence on respiration. However, according to the lastest information, use of nitrous oxide for more than 2 h is counterproductive since it causes a severe reduction of methionine synthesis, which in turn can cause a severe decrease in the level of vitamin B_{12} with all its subsequent consequences.

Synthesis of nitrous oxide

Nitrous oxide is synthesized either by the thermal decomposition of ammonium nitrate or by the oxidation of sulfamic acid by nitric acid.

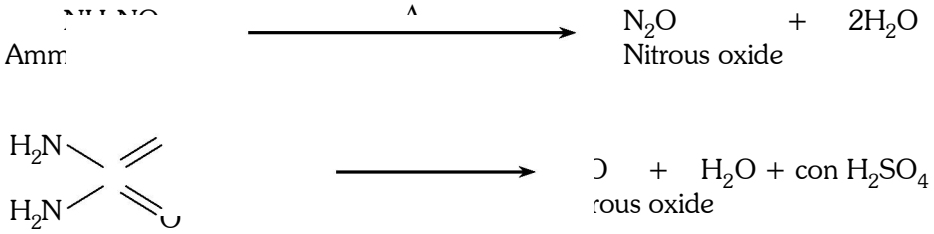


Fig.: Synthesis of nitrous oxide

Short Question and Answers

1. Draw the structure of dapsone and its preparation and therapeutic activity.

Ans :

Dapsone:

Dapsone is used to treat leprosy. Lesions of the skin, loss of sensitivity to pain, and superficial nerves are the three main signs of leprosy, a disease caused by the mycobacteria Mycobacterium leprae. This disease is extremely infectious. Children and men are more susceptible to it then women. The incubation period can last several years, which makes early detection of leprosy difficult. Chemotherapy of leprosy consisted of taking dapsone, which gave good clinical results. However, because of the primary and secondary resistance that originated from prolonged use, it is now necessary to use a certain combination of drugs. Currently, dapsone is used along with rifampin and clofazimine. Ethionamide is also prescribed.

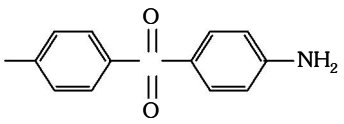


Fig.: Dapsone

Dapsone, which was first proposed in 1941, possesses both bactericidal as well as bacteriostatic acitivity with respect to Mycobacterium leprae and Mycobacterium tuberculosis. It is used to treat patients with herpetiform dermatitis. It is believed that the mechanism of its action consists of competitive inhibition of the enzyme dihydroprotease synthetase, which blocks synthesis of folic acid in microorganisms, allowing it to also be viewed as an analog of p-aminobenzoic acid. Synonyms of this drug are avosulfon, croysulfon.

Synthesis of Dapsone

Dapsone, 4,4-diaminodiphenylsulfone, is synthesized either from 4-chloronitrobenzene (Method - I) or from the sodium salt of 4-acetamidobenzenesulfonic acid (Method - II).

Method-I

Reacting 4-chloronitrobenzene with sodium sulfide gives 4,4-dinitrodiphenylthioether, and oxidation of the sulfur atom in this compound using potassium dichromate in sulfuric acid gives 4,4-dinitrodiphenylsulfone. Reduction of the nitro group in the resulting compound using tin dichloride in hydrochloric acid makes the desired dapsone. It has also been suggested to reduce the nitro group to an amino group, protect it with an acetyl protection, oxidize the sulfur atom to a sulfone using potassium dichromate, and then remove the acetyl protective group by hydrolysis.

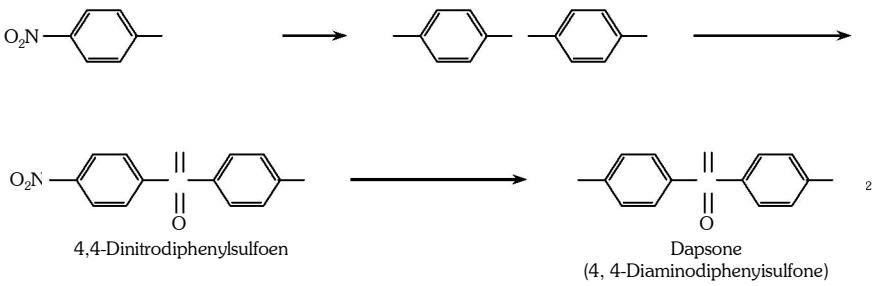


Fig.: Synthesis of dapsone (Method-I)

2. Draw the Pencillins structures.

Ans :

The term 'penicillins' represent a group of comounds with closely related structures. One of the most important discoveries in the 20th century was the discovery of penicillin, which was discovered in 1928 by Alexander Flemming, an English bacteriologist. The two natural penicillins obtained from culture filtrates of penicillium notatum or the closely related species P chrysogenum are penicillin G and the more acid-resistant penicillin V. They are active only against Gram-positive bacteria (which have a thick layer of peptidoglycan in the wall) and not against Gram-negative species, including many serious pathogens like Mycobacterium tuberculosis (the cause of tuberculosis).

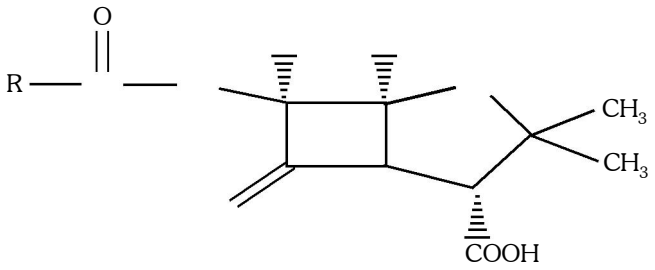


Fig.: Penicillins

3. Explain the synthesis of Antic cancer cisplatin and its therapeutic activity.

Ans :

Cisplatin

Cisplatin is a non-organic platinum-containing drug with alkylating properties. It causes cross-linking of DNA and RNA chains. Cisplatin, like other alkylating agents, bind primarily at N7 of two neighbouring deoxyguanylates to DNA, which inhibits its replication. It is only used intravenously. It is highly reactive with carcinomas of the testicles, ovaries, head, neck, spleen, lungs, and so on. Synonyms of this drug are platinol, platiblastin, platinex, neoplatin, and others.

Synthesis of Cisplatin

Cisplatin, cis-diaminodichloroplatinum, is made by reducing potassiumhexachloroplatinate by hydrazine to potassium tetrachloroplatinate, which reacts with ammonia to give cisplatin.

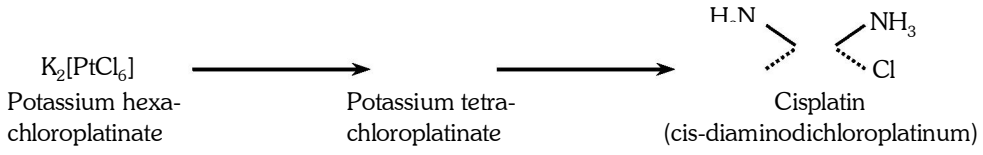


Fig.: Synthesis of cisplatin

4. Define Anesthetics.

Ans :

An anestheic is a drug used to induce anesthesia - in other words, to result in a temporary loss of sensation or awareness. Generally an ideal anesthetic should have the following characteristics. It should be:

(i) Non-inflammable

(ii) Inexpensive

(iii) Require uncomplicated equipment for administration

(iv) Provide sufficient muscular relaxation

(v) Have no effect on the myocardium or respiration at anesthetic doses

(vi) Chemically and metabolically stable

(vii) Sufficiently potent to permit adequate oxygen supply, and

(viii) Have a wide margin of safety.

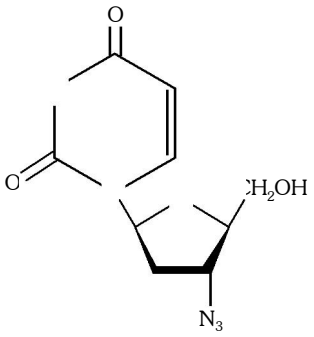
5. Write the synthesis and therapeutic activity of AZT.

Ans :

AZT (azidothymidine) or ZDV (Zidovudine)

AZT (azidothymidine) also known as Zidovudine (ZDV) is a thymidine analogue. It is 1-(3-azido-2,3-dideoxyb-D-erthyro-pentofuranosyl)-5-methylpyrimidine-2,4-(1H, 3H)-dione. Zidovudine is an antiretroviral drug that is clinically active againstt HIV-1 and is intended to treat HIV-infected patients. Zidovudine is an analog of thymidine that inhibits replication of the AIDS virus. It also turned into mono-, di-, and triphosphates by the same cellular enzymes that catalyze phosphorylation of thymidine and thymidine nucleosides. Zidovudine-triphosphate is then included in the terminal fragment of the growing chain of viral DNA by viral reverse transcriptase, thus causing the viral DNA chain to break apart in cells infected with the virus.

Zidovudine has been authorized for treating patients with AIDS. It significantly prolongs the life of the patient, although it has a number of toxic effects. Synonyms of this drug are azidothymidine and retrovir.



Synthesis of AZT (Zidovudine)

Zidovudine is 3-azido-3-deoxythymidine, is synthesized from 1-(2-deoxy-5-O-trityl-β-D-lyxosyl) thymine, which is treated with methane sulfonyl chloride in pyridine to make the corresponding mesylate. Replacing the mesyl group with an azide group using lithium azide in dimethylformamaide makes the product with inverted configuration at C3 of the furnaosyl ring. Heating this 80% acetic acid removes the trityl protection, giving zidovudine.

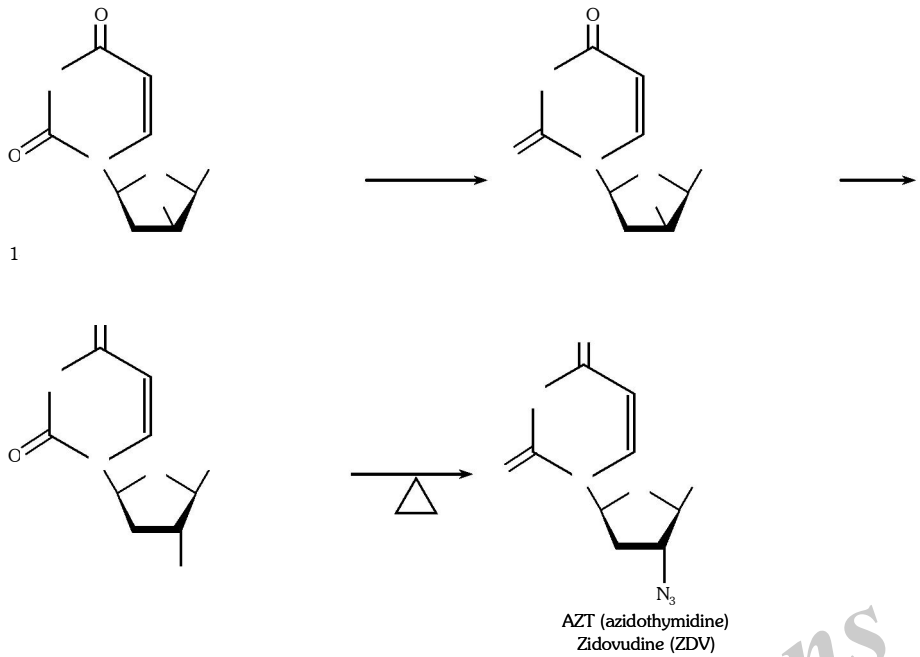


Fig.: Synthesis of AZT (azidothymidine) or Zidovudine (ZDV)

6. Discuss the Benzocaine local anaesthetic.

Ans :

Local Anesthetics

The anesthesia produced by local anesthetics is generally without loss of consciousness or the impairment of vital central functions. For this reason, local anesthetics play a key role clinically in dentistry and in other minor surgeries for temporary relief from pain. Local anesthetics are drugs that cause a state of loss of sensation by reversible blocking the nerve impulses that transmit the feeling of pain from the particular local area to the brain. Benzocaine (Topical), Lidocaine (Topical and Parenteral), Butacaine (Topical), Butamben (Topical), and Procaine (Parenteral) are among the some of the local anesthetics.

Benzocaine

Benzocaine is used in topical anesthesia on the skin and mucous membranes in the form of aerosols, or as creams for reduction of pain caused by itching, cuts, bites, etc. It begins to work 15-30 sec after application and lasts 12-15 min. It is also used under the names anestezin, dermoplast, and others.

Synthesis of Benzocaine

Benzocaine is the ethyl ester of 4-aminobenzoic aicd. The classic, optimal way of benzocaine synthesis is the reduction of the nitro group of the ethyl ester of 4-nitrobenzoic acid to benzocaine by hydrogen, which generates directly in the reaction medium by the reaction of iron filings with dilute acids.

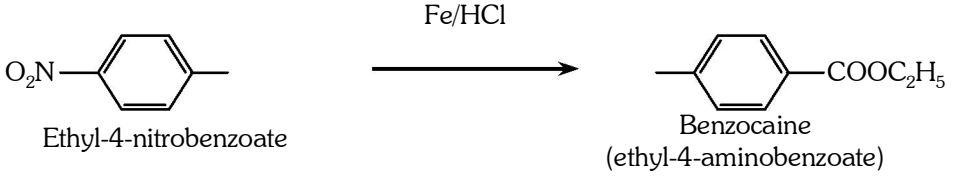


Fig: Synthesis of benzocaine or eythl-4-aminobenzoate

7. Synthesis of Nitrous oxide.

Ans :

Nitrous Oxide

Nitrous oxide, which is also called laughing gas, is a weak anesthetic. It is usually used together with hypnotics, analgesics, and muscle relaxants. It is sometimes called an ideal anesthetic because of the absence of any kind of suppressive influence on respiration. However, according to the lastest information, use of nitrous oxide for more than 2 h is counterproductive since it causes a severe reduction of methionine synthesis, which in turn can cause a severe decrease in the level of vitamin B_{12} with all its subsequent consequences.

Synthesis of nitrous oxide

Nitrous oxide is synthesized either by the thermal decomposition of ammonium nitrate or by the oxidation of sulfamic acid by nitric acid.

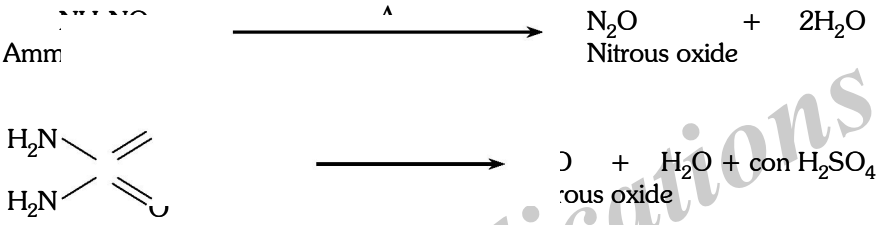
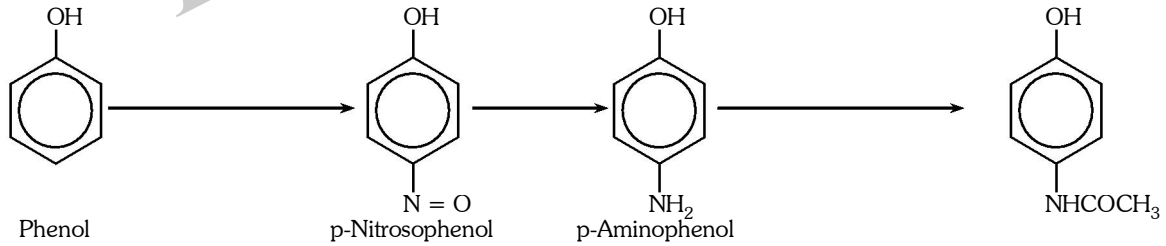


Fig.: Synthesis of nitrous oxide

8. Write the Synthesis of Paracetamol.

Ans :

Method A (from phenol) Nitrosation of phenol gives 4-nitrosophenol which, on reduction, yields 4-aminophenol as a drug intermediate. This compound, on selective acetylation (acetylation of the amino group but not the hydroxy group), results in paracetamol.



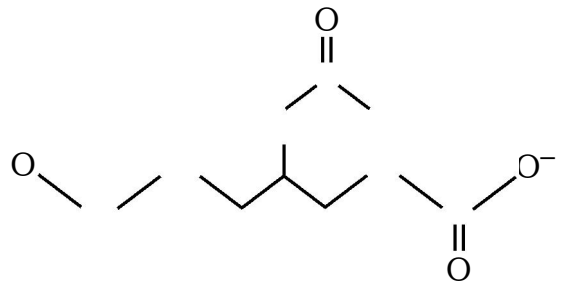
Synthesis of paracetamol starting from phenol.

9. Give the cardiovascular drugs with examples.

Ans :

Glyceryltrinitrate

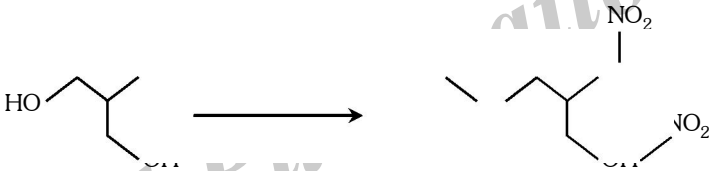
1. Nitroglycerin also known as glycerylnitrate is a medication used for heart failure, high blood pressure and to treat and prevent chest pain from not enough blood flow to the heart or due to cocaine.
2. It used as chest pain from a heart attack.



Nitroglycerin an organic nitrate is available in many forms as a vasodilator.

Mechanism of action

- Nitroglycerin is converted to nitric oxide (NO) an active intermediate compound which activates the enzyme.
- This stimulates the synthesis of cyclic guanosino 3', s' - monophosphate (CGMP) which then activates a series of protein kinase - dependent phosphorylation of the myosin light chain of the smooth muscle fiber.
- The subsequent release of calcium ions result in the relaxation of the smooth muscle cells and vasodilation.



Choose the Correct Answers

1. The drug used to treat malaria _____. [b]

   (a) Isoniazid (b) Chlaroquin

   (c) Paracetamol (d) Aspirin

2. Aspirin and Paracetamol shows _____ activity. [c]

   (a) Antipyretic (b) Analgesic

   (c) Both a and b (d) None of the above

3. Omeparazole contains two heterocyclic moities. [a]

   (a) Benzlmidazole + Pyridine

   (b) Benzimidazole + Benzene

   (c) Benzimidazole + Phenol

   (d) None of the above

4. Active Ingredient of benzocaine [c]

   (a) Benzene

   (b) Ethyl 4-Nitro Benzeno

   (c) Ethyl-4-Amino Benzene

   (d) 4-Anonobenzene

5. _____ Drugs were extensively used during world war II to prevent infections in wounds.[c]

   (a) A (b) B

   (c) Sulphonamids (d) N

6. _____ Species which gives higher yield of pencillin [b]

   (a) Pencillin notatum (b) Pencillium chrysogenum

   (c) Both a and b (d) None of the above

7. On selective acetylation of P-Amino phenol gives _____ [a]

   (a) Paracetamol (b) Aspirin

   (c) Isoniazied (d) Dapson

8. the active partin pencillin is _____ [a]

   (a) β-Lactum ring (b) α-Lactum ring

   (c) Both a and b (d) Nill

9. Chlorosulphonation of Acetanlide yields _____ [d]

(a) Dopsone (b) Paracetamol

(c) Aspirin (d) Sulphanlamide

10. Isoniazid inhibits the _____ acid of wall of mycobacteria [b]

(a) Malonic acid (b) Mycalic acid

(c) Acetylcholire (d) Acetic acid

Fill in the Blanks

1. Dapsone is used to treat _____.
2. The drug which is used to treat anticancer _____.
3. Nitrous oxide is used as _____.
4. The drug used to treat for AIDS _____.
5. Methyl salicylate is known as _____.
6. The drug inhibiting $H^+|k^+$ ATP ase in Stomach is _____.
7. Tuberculosis is caused by _____ microorganism.
8. _____ drug lowers the blood sugar level in diabetic patients.
9. Temparary loss of sensaiton or awareness cuased by _____.
10. _____ is used for heart failure, high blood pressure.

ANSWERS

1. Laprosy
2. Cisplatin
3. Anesthetic
4. Zidovudine
5. Aspirin
6. Omeprazole
7. Mycobacterium tuberculosis
8. Tolbutamide
9. Anesthetics
10. Glycerylnitrate

UNIT - IV

(Medicinal Chemistry)

Molecular Messengers, Vitamins and Micronutrients

S6-E-A-IV: Molecular Messengers: Introduction to hormones and neurotransmitters, Thyroid hormones, Antithyroid drug-Carbimazol. Adrenaline: Adrenergic drugs-salbutamol, atenelol.

Serotonin: SSRIs-fluoxetine. Dopamine: Antiparkinson drug- Levodopa.

Vitamins and Micronutrients

Introduction, Vitamin sources, Difficiency disorders and Remedy of Vitamins A, B, C, D, E, K and Micronutrients - Na, K, Ca, Cu, Zn and L.

Molecular Messengers, Vitamins and Micronutrients

Q1. What are harmones.

Ans :

Hormones are chemical messengers secreted in small quantities (nanograms to milligrams per day) by ductless glands called the endocrine glands of the body. Unlike vitamins, hormones are produced in the human body. The pituitary. Parathyroid, thyroid, adrenal, pancreas are some of the endocrine glands present in humans. Hormones perform varied physiological functions: increase or decrease the rate of reaction, control growth, metabolism and reproduction, and many other functions of the body.

Structurally, all hormones are not alike; they have diverse structure just like vitamins. They may be classified according to structure:

i) Amino acid (L-tyrosine) based hormones, e.g., Thyroxin

ii) Polypeptide and protein-based hormones, e.g., Insulin

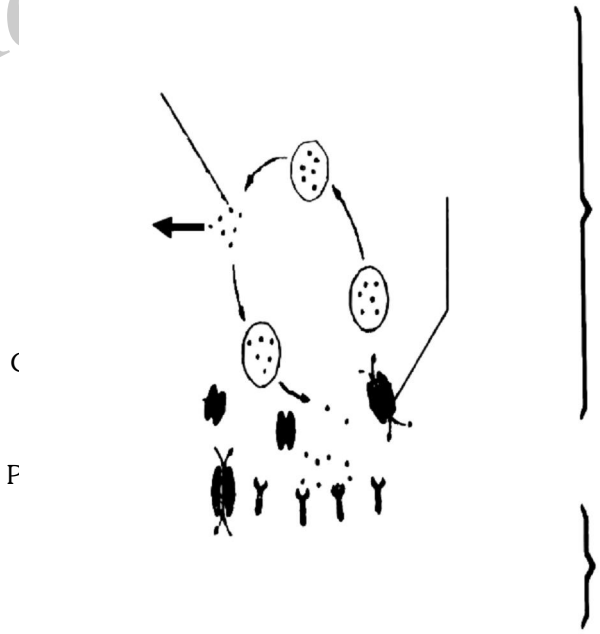
iii) Steroidal hormones, e.g., Testosterone

Q2. What are neurotransmitters.

Ans :

Neurotransmitters:

1. Neurotransmitters are endogenous chemicals thai enable neurotransmission It is a type of chemical messenger which transmits signals across a chemical synapse, such as a neuromuscular junction, from one neuron (nerve cell) to another "target" neuron, muscle cell, or gland cell.



2. Electrical signals do not cross the gap between most neurons. They are changed into chemical signals to cross the gap between most neurons so they are changed into chemical signals to cross the gap.

3. Neurotransmitters are released from synaptic vesicles in synapses into the synaptic cleft, where they are received by neurotransmitter receptors on the target cells.

4. Many neurotransmitters are synthesized from simple and plentiful precursors such as amino acids, which arc readily available from the diet and only require a small number of biosynthctic steps for conversion.

5. Neurotransmitters play a major role in shaping everyday life and functions. Their exact numbers are unknown, but more than 200 chemical messengers have been uniquely identified

Importance

Neurotransmitters are the brains chemical that communicate information throughout your brain and body. They relay information between neuron to neuron. Neurotransmitters communicate messages to heart to beat, lungs to breath, and stomach to digest, ft also affects mood, sleep, concentration, etc. Without neurotransmitters your brain would fail to utilize serotonin, dopamine, norepinephrine and much more needed chemicals that is vital to both brain and body.

Q3. Mention the thyroid harmones.

Ans :

Thyroxine (amino acid based)	Thyroid Triiodothyonina (T_3)	Regulates the rate of oxygen consumption and cellular metabolism (goitre).

Q4. Write the synthesis of antithyroid drug carbimazol.

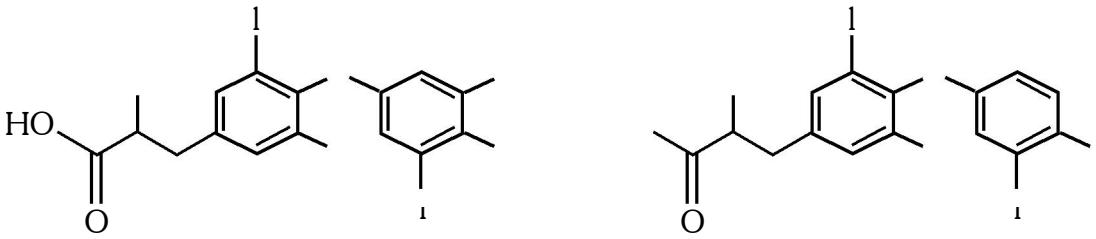
Ans : **(Imp.)**

Thyroid hormone:

1. Thyroid hormone: A chemical substance made by the thyroid gland for export into the bloodstream. The thyroid gland needs iodine to make thyroid hormones. The two most important thyroid hormones are thyroxine (T_4) and triiodothyronine (T_3). The thyroid gland is located just in front of the trachea in neck part or region.

2. These two hormones produced and released by the thyroid gland, namely triiodothyronine (TO and thyroxine (T_4). They are tyrosine-based hormones that are primarily responsible for regulation of metabolism. T_3 and T_4 are partially composed of iodine. The deficiency of iodine leads to decreased production of T_3 and T_4, enlarges the thyroid tissue and will cause the disease known as simple goitre. The major form of thyroid hormone in the blood is thyroxine (T_4), which has a longer half-life than T_3

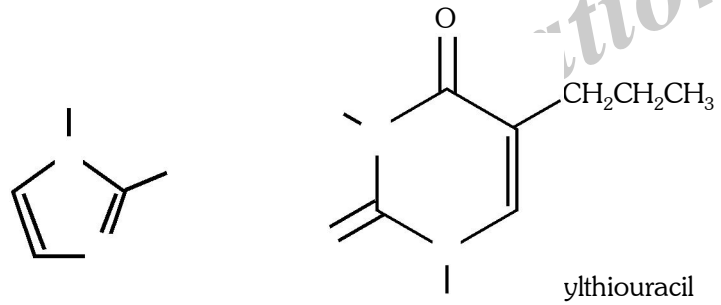
Thyroid Hormones



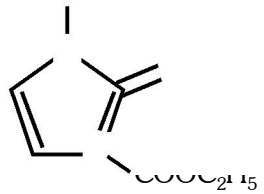
Thyroxine (T4) Triiodothyronine (T3)

Anti thyroid drug

The ant thyroid drugs include carbimazole, methimazole, propylthiouracil (PTU). These drugs are used to treat hyperthyroidism (overactivity of the thyroid gland). These drugs reduce the excessive thyroid activity and thereby avoids surgery.



ylthiouracil



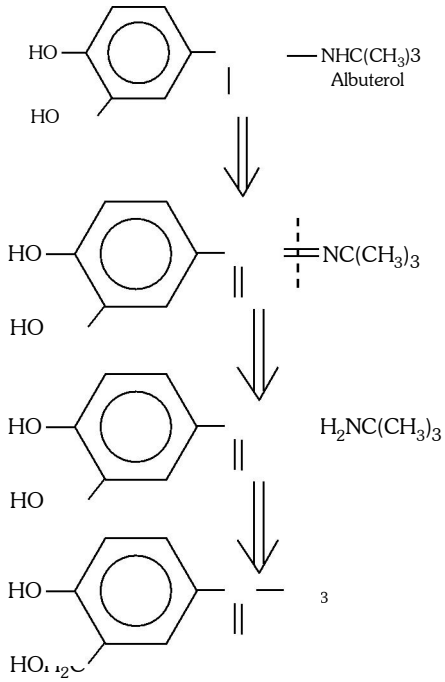
Carbimazole

Q5. Mention the adrenergic drugs synthesis and Therapeutic activity. Discuss the synthesis of atenelol and salbutamol.

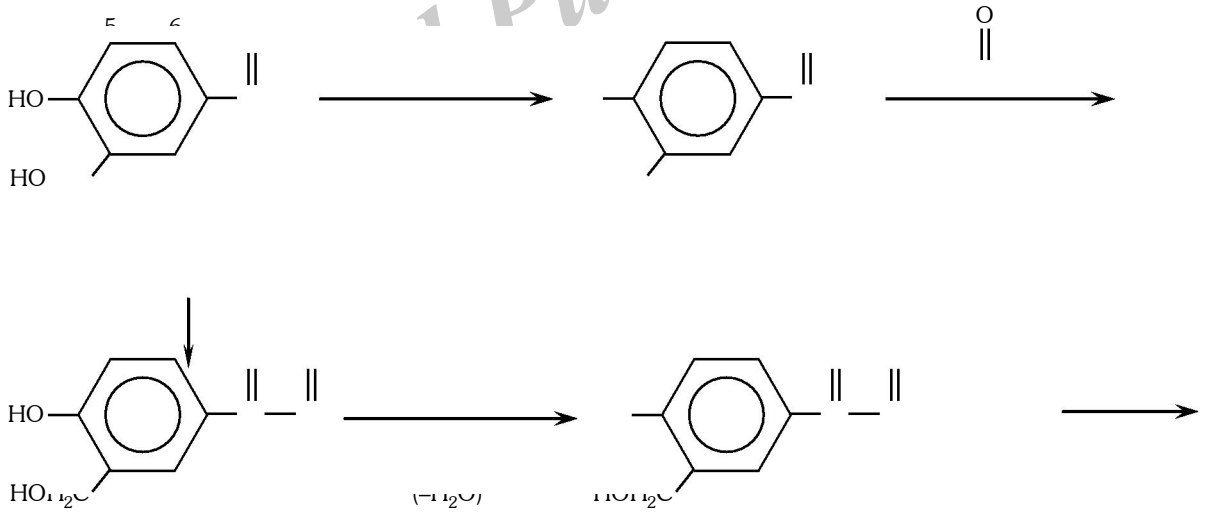
Ans : **(Imp.)**

Albuterol (Salbutamol): a bronchodilator

Albuterol is 2-(tert-butylamino)-1-(4-hydroxy-3-hydroxymethylphenyl)-1- ethanol, also known as salbutamol. The structure and synthetic plan of salbutamol are represented in Figure.



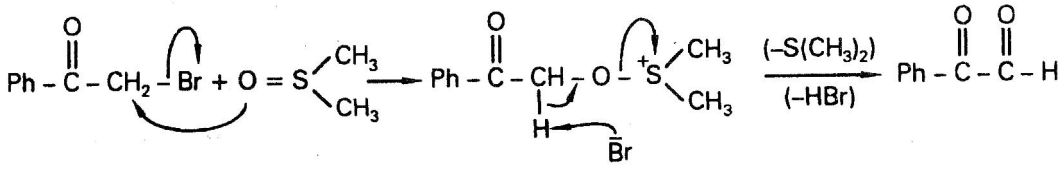
Synthesis salbutamol is synthesized from 4-hydroxy-3 (hydroxymethyl) acetophenone. The synthesis sequentially involves: (i) bromination,



2[4-Hydroxy-3-(hydroxymethyl)-phenyl]-2-oxo-ethanal

(ii) Oxidation, (iii) the formation of an imine, and (iv) hydrogenation.

Oxidation mechanism of 2- bromo-1-(hydroxymethyl)-phenyl] ethanone with dimethylsulphoxide (DMSO).



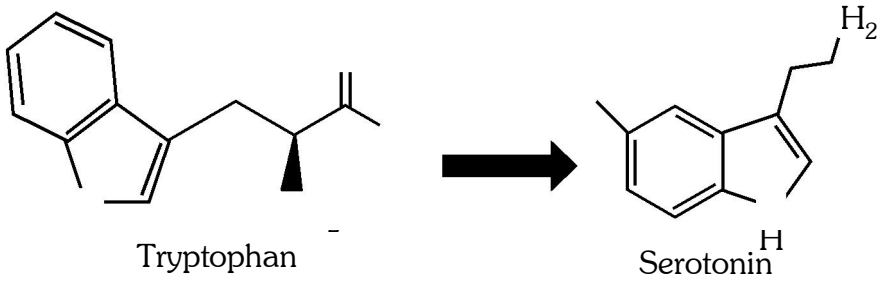
Therapeutic activity salbutamol is a sympathomimetic (adrenergic) agent. It acts as a β-2 adrenergic receptor agonist situated in the bronth. It inhibits bronchail spasms and is very effective in the treatment of bronchail asthma; it us a bronchodilator.

Q6. Write the synthesis and therapeutic activity of serotonin.

Ans :

Serotonin:

1. Serotonin is a chemical nerve cells produce. It sends signals between your nerve cells. Serotonin is found mostly in the digestive system, although it's also in blood platelets and throughout the central nervous system.
2. Serotonin is made from the essential amino acid "tryptophan". This amino acid must enter our body through our diet and is commonly found in foods such as nuts, cheese, and red meat.
3. Tryptophan deficiency can lead to lower serotonin levels. This can result in mood disorders, such as anxiety or depression.



Selective serotonin reuptake inhibitor (SSRI)

1. A selective serotonin reuptake inhibitor (SSRI) is a type of anti-depressant medication.
2. SSRIs block the reabsorption (reuptake) of serotonin in the brain, making more serotonin available. SSRIs are called selective because they seem to primarily affect serotonin, not other neurotransmitters. SSRIs also may be used to treat conditions other than depression, such as anxiety disorders.
3. E.g., paroxetine (brandname Paxil), fluoxetine (brandname Prozac) sertraline (brandname Zoloft).
4. Fluoxetine is an oral drug that is used primarily for treating depression.

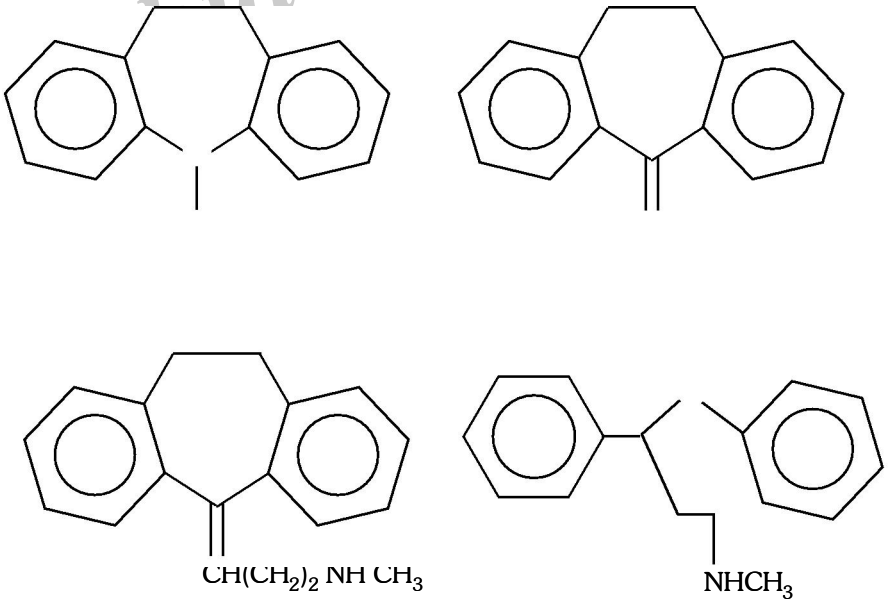
5. Fluoxetine is a racemic mixture of the R and S enantiomers and are equivalent pharmacologic activity.
6. Fluoxetine used to treat major depressive disorder (MDD), moderate to severe bulimia nervosa, obsessive-compulsive disorder (OCD), premenstrual dysphoric disorder (PMDD), panic disorder with or without agoraphobia and in combination with olanzapine for treatment-resistant or bipolar I depression.
7. According to the amines hypothesis, a functional decrease in the activity of amines, such as serotonin and norepinephrine, would result in depression; a functional increase in the activity of these amines would result in mood elevation.

Q7. Explain the SSRIS of fluoxetine and dopamine.

Ans : **(Imp.)**

Fluxetine

Antidepressants are drugs that are used on patients who suffer from acute mental depression. These drugs are CNS stimulants as they elevate the mood and generally have no effect on normal persons. They do Have side effects such as dryness of the mouth, blurred vision, constipation and urinary problems. Because of their sedative effect, they are usually used at bedtime. Antidepressants include (i) imipramine (82), (ii) amitriptyline (83), (iii) nortriptyline (84) and (iv) fluoxetine (prozac) (85). Nortriptyline, which is a metabolic product of amytriptyline, is twice as potent as an antidepressant. Fluoxetine (prozac) (85) is also known as the "Happiness pill". The chief advantage of fluoxetine is that it does not cause significant cardiovascular side effects or weight-gain.

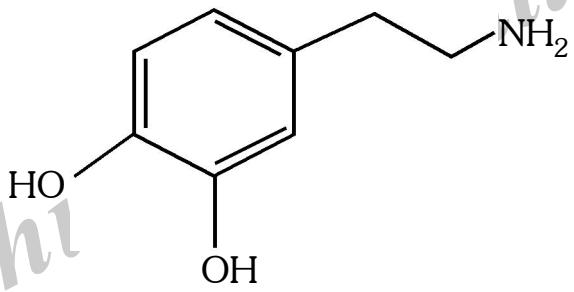


Nortriptyline (84)
(Aventil)

Fluoxetine (85)
(Prozac)

Mechanism of action

1. It works by blocking the absorption of the neurotransmitter serotonin in the brain.
2. Regulating the amount of serotonin helps brain cells transmit messages to each other. This results in a better and more stable mood.
1. Common side effects: Sleep problems (insomnia), strange dreams; headache, dizziness, vision changes; tremors or shaking, feeling anxious or nervous pain, weakness, yawning, tired feeling; upset stomach, loss of appetite, nausea, vomiting, diarrhoea; dry mouth, sweating, hot flashes
2. Dopamine (3,4-dihydroxyphenylethylamine), differs from the other naturally occuring catchcholamine, lacking the –OH group on the ethylamine side chain. It is the metabolic precusrsor of noradrenaline and adrenaline and is a central neurotransmitter.
3. It is one of the catchcholamine neurotransmitter in the brain. It is derived from tyrosine and is the precursor to norepinephrine and epinephrine.
4. Dopamine is a major transmitter in the extrapyramidal system of the brain, and important in regulating movement. A family of receptors (dopmaine receptors) mediate its action.



Mechanism of action

1. Dopamine is a substrate for both MAO and COMT and is thus ineffective orally. It has minimal effects on the CNS, not crossing the blood brain barrier. Dopamine exerts a positive inotropic effect on the heart, acting at a I receptors. Dopamine usually increases the systolic and pulse pressures.
2. Dopamine is a precursor to norepinephrine in noradrenergic nerves and is also a neurotransmitter in certain areas of the central nervous system.
3. Dopamine produces positive chronotropic and inotropic effects on the myocardium, resulting in increased heart rate and cardiac contractility. This is accomplished directly by exerting an agonist action on beta-adreno receptors and indirectly by causing release of norepinephrine from storage Sites in sympathetic nerve endings. In the brain, dopamine acts an agonist to the five dopamine receptor subtypes (D1, D2, D3, D4. D5).

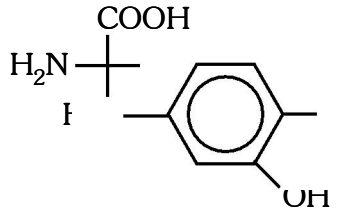
Q8. Discuss the synthesis of anti-parkinson drug levodopa.

Ans : **(Imp.)**

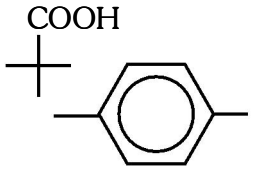
L-dopa - cures Parkinsons Disease

L (or S) - dopa is active whereas D (or R) - dopa is toxic

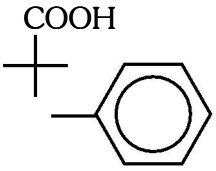
L-Dopa (Dihydroxyphenyl alanine) is systematically known as (L)3-3(3,4- dihydroxy-phenyl)-2-aminopropa propanoic acid. Structurally, it resembles the naturally occurring amino acids, L-tyrosine and L- phenylalanine. The Fischer- projection formulae of the these three compounds are represented below.



L-Dopa
(3-Hydroxy-L-tyrosine)

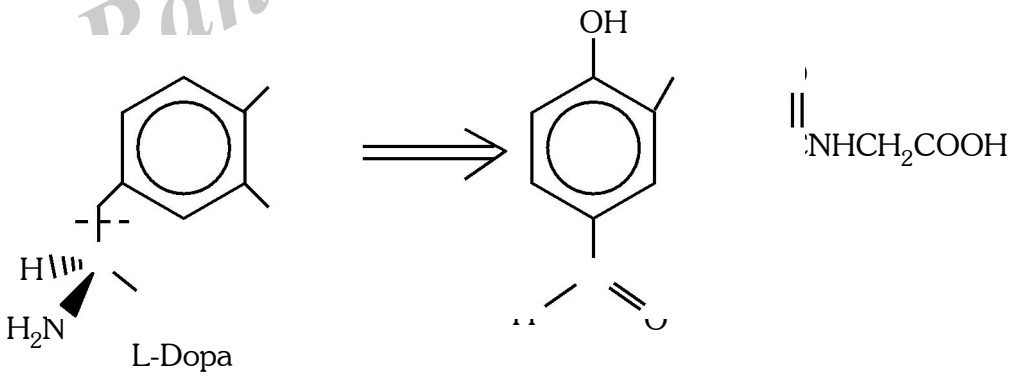


L-Tyrosine
(an amino acid)



L-Phenylalamine
(an amino acid)

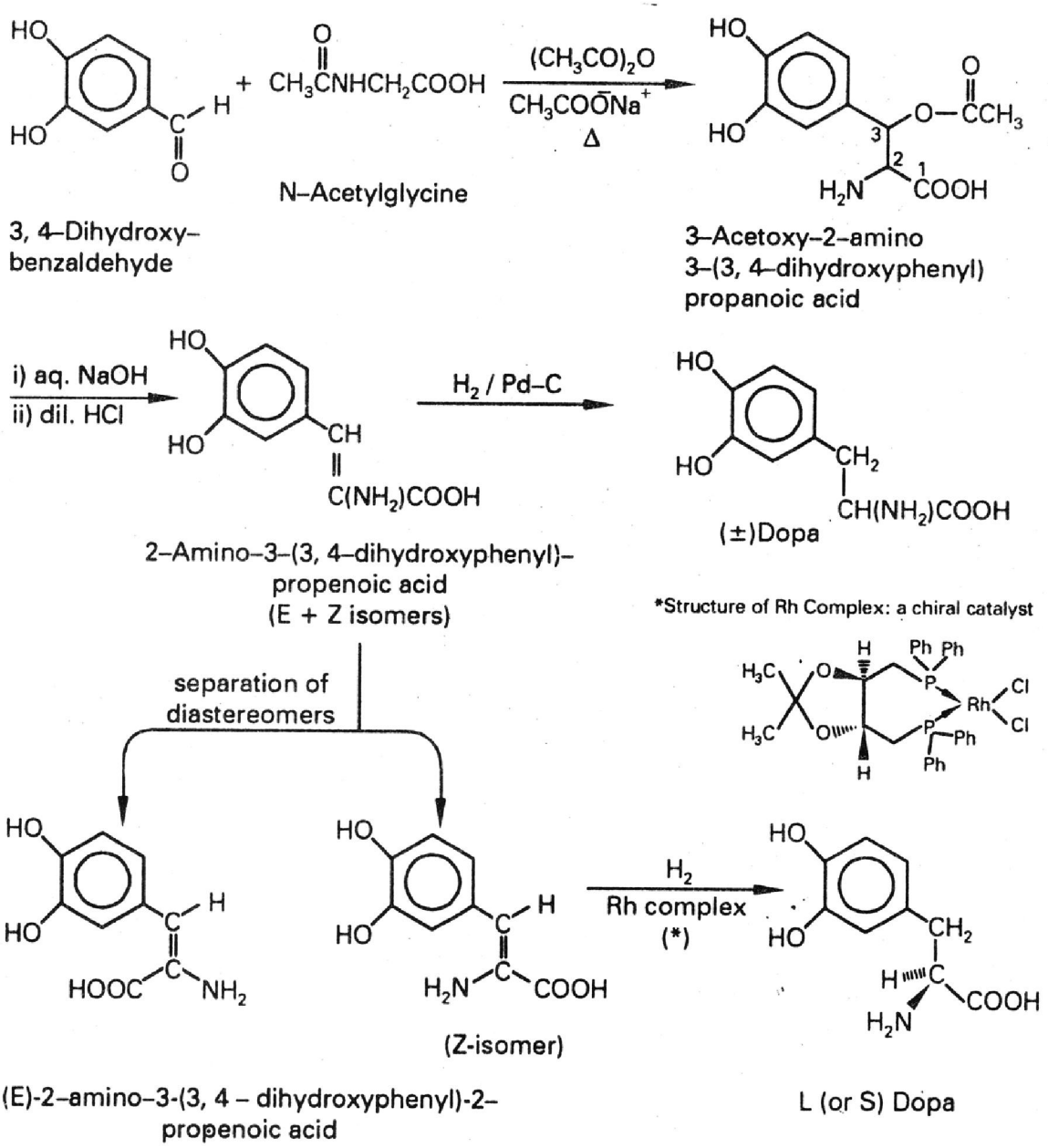
L-dopa has one chiral carbon. In terms of absolute configuration, it is called (S)-3(3,4-dihydroxphenyl)2-aminopropanoic acid (S-dopa). since (S)-dopa is levorotatory, it is also referred to as (S)(-)-dopa.



L-Dopa

Synthetic Plan for L-Dopa

Synthesis L-dopa is synthesized from 3,4-dihydroxybenzaldehyde and N-acetyl glycine by the perkin type of condensation, followed by saponification (basic hydrolysis of an ester group). Dehydration of the intermediate yield a mixmture of geometric isomers (E/Z isomers). Hydrogenation of the mixmture, using H_2\pd-c (catalyst, gives the racemic



Synthesis of L-Dopa

dopa Hydrogenation of the Z-isomer, obtained in the pure state after separation, using a chiral catalyst (Rhodium complex), gives (S)-dopa (L-dopa) selectively. This is an example of asymmetric synthesis (the synthesis of an optically active produce from achiral starting material using an optically a active reagent and\or catalyst, is known as asymmetric synthesis).

Therapeutic activity L-dopa cures parkinson's disease caused by the deficiency of dopamine, which is one of the neurotransmitters in the brain.

Q9. Explain briefly about Vitamins, Hormones and Synthetic Drugs

Ans : **(Imp.)**

Introduction

The average life expectancy of human beings has been on the rise. One of the major reasons for this is the widespread use of drugs. Over the past hundred years, the most remarkable application is the increasing use of organic compounds as drugs. The term chemotherapy (shorter version of chemical therapy) is generally used for the treatment of diseases by chemicals, caused due to microbial infections. Drugs are broadly classified into three groups:

i) Chemotherapeutic drugs;

ii) Pharmacodynamic agents;

iii) Vitamins and hormones

In this chapter, a brief account of vitamins and hormones is given. The synthesis of some of the common drugs and their therapeutic uses are presented. Penicillin, as an example of a natural drug, is also described.

The synthesis and mechanism of action of two chemotherapeutic drugs of the class of antibacterials are described in this chapter.

Vitamins

The term 'vitamine' is derived from the word vital (meaning life)and amine. As the first discovered members of this class of compounds contain amino groups, these were named vitamines. Later, it was found that all of them do not have amino groups. Hence, the letter 'e' was deleted from vitamine. Now, it is spelled as vitamin. Vitamins are a class of nutrients / dietary factors that can not be biosynthesized by the human body (except D2) and are supplied through our diet. These are essential for the normal functioning of the body, and are produced by plants. Some of the vitamins are synthesized while others are extracted from microorganisms.

The human body needs vitamins in balanced proportions and in small quantities. The deficiency of a particular vitamin causes a specific disease(s). The treatment of deficiency diseases by supplementing the diet with the necessary vitamins is known as vitamin therapy. Therefore, vitamins can be considered as drugs if they fall short in the body; otherwise, they are nutrients.

On the other hand, an excess consumption of vitamins may cause side effects (hyper-vitaminosis). For example, an excess of vitamin A causes irritability and dry skin. An overdose of vitamin D can cause pain in the bones. Extra amounts of fat-soluble vitamins are stored in the fatty tissues, especially in the liver; water-soluble vitamins tend to be excreted.

Classification of vitamins

On the basis of solubility in fat or water, vitamins are broadly divided into **fat-soluble vitamins** (lipophilic) and **water-soluble vitamins** (hydrophilic), respectively. Vitamins A, D, E and K are fat-soluble; whereas vitamins B-complex and C, are water-soluble. The structure of the former class of

vitamins consists of a higher portion of hydrocarbon and less polar group(s), thus making them fat-soluble. The latter group of vitamins have a larger number of polar groups and, hence, are soluble in water (fats are less polar than water).

Structure, biochemical functions, deficiency diseases and sources of vitamins

The structures of various vitamins have been established. Vitamin D2 is produced in the skin from ergosterol (a steroid) on exposure to sunlight. For this reason, vitamin D is some times called the sunshine vitamin. (There is a misconception that vitamin D is present in sunlight). The structures of some of the vitamins along with their biochemical functions, diseases caused due to deficiency, and sources are presented.

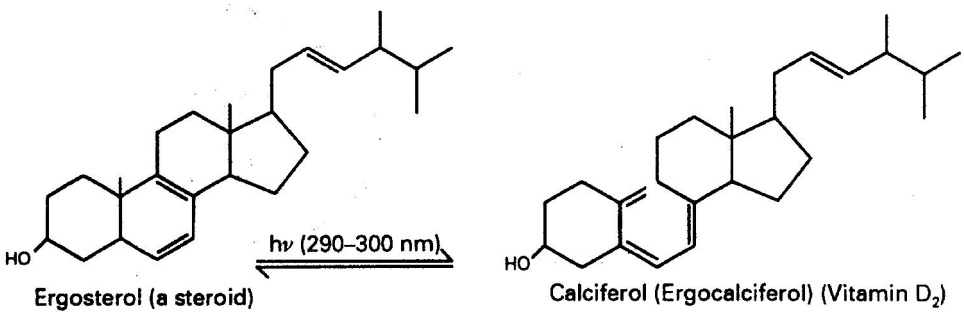
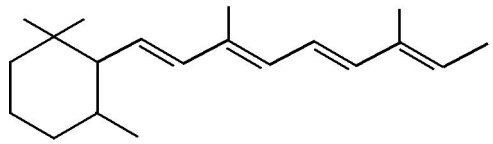
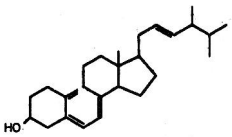
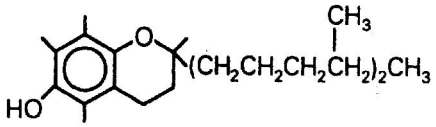


Fig.: Isomerization of Ergosterol to Vitamin D_2 in the presence of light.

Table : Names, Structures, Biochemical Functions, Deficiency Symptoms and Sources of some Vitamins

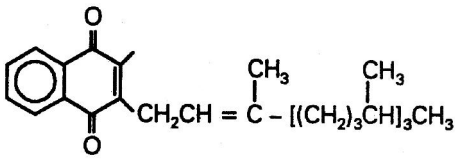
Names and Structures of Vitamins	**- Biochemical Functions - Deficiency Effects - Sources**
A. Fat-soluble Vitamins	
Retinol (Vitamin A) 	- Prevents night blindness by regeneration of rhodopsin (visual purple) and protects the eye from infection - Deficiency causes light sensitivity, night blindness, xerophthalmia - Fish, liver, eggs, butter, cheese; β- carotene in carrots is a provitamin (vitamin precursor)
Calciferol (Vitamin D_2) 	- Aids in Ca and P metabolism and is essential in building strong bones - Deficiency causes rickets - Cod liver oil, irradiated ergosterol (vitamin D) as a milk supplement

a-Tocopherol (Vitamin E)



- Antioxidant (prevents oxidation, e.g., of fats), maintains RBC membranes
- Oedema and anemia in infants; sterility (Vitamin E is often called the *antisterility vitamin*, as it is responsible for normal reproductive function)
- Wheatgerm oil, green vegetables, egg- yolk, meat, nuts

Phylloquinone (Vitamin K_1)

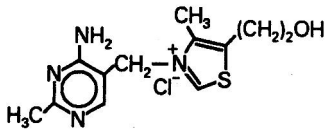


- Aids in synthesis of prothrombin (blood coagulant) Slows clotting of blood and hemorrhage
- Cauliflower, leafy vegetables o

B. Water-soluble vitamins

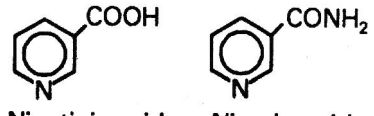
B-Complex

Thiamine (Vitamin B_1)



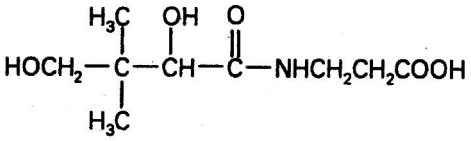
- Carbohydrate metabolism, proper functioning of heart and circulatory system
- Deficiency causes beriberi (i.e., polyneurities, resulting in muscle paralysis; enlargement of the heart, and finally heart failure)
- Cereal grains, legumes, milk, nuts

Niacin (Vitamin B_3)



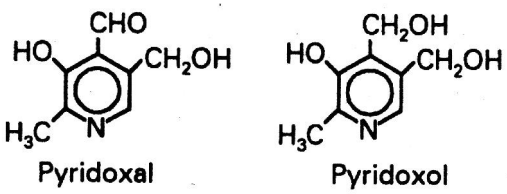
- Metabolism of carbohydrates, fats and proteins
- Deficiency causes pellagra (symptoms are diarrhea, dermatitis and dementia (loss of memory)
- Yeast, liver, peanuts, soyabeans, potatoes

Pantothenic acid (Vitamin B_5)

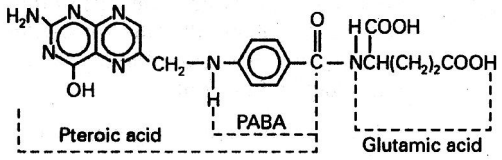
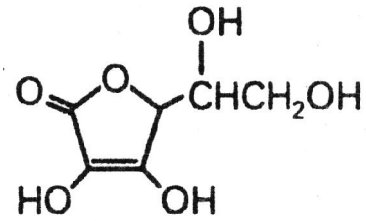


- Useful in the synthesis of sex hormones, heme, cholesterol, fatty acids, amino acids
- Causes retarted growth, gastrointestinal disturbances, (possibly) emotional problems
- Yeast, mushrooms, egg-yolk, nuts, liver

Vitamin B_6



- Necessary for growth and healthy nervous system cho
- Causes dermatitis, irritability and increased susceptibility to infections, weakness
- Egg, liver, yeast, peas, beans, milk

Folic acid (Vitamin B_9) 	-	Coenzyme related to growth, important in proper development of RBC
	-	Causes anemias (treatment of megaloblastic anemia, characterized by RBC)
	-	Liver, kidney, mushrooms, yeasty green leafy vegetables
Ascorbic acid (Vitamin C) 	-	Act as a reducing agent, complexes with metal ions, resists disease, helps in healing wounds
	-	Causes scurvy (symptoms are swollen legs, red-spotted skin, rotten gums, black lungs and damaged liver)
	-	Citrus fruits, tomatoes, green pepper

Q10. Write about Micro and Macro nutrients.

Ans : **(Imp.)**

Micronutrients are one of the major groups of nutrients our body needs. They include vitamins and minerals.

Vitamins are necessary for energy production, immune function, blood clotting and other functions. Minerals play an important role in growth, bone health, fluid balance and several other processes.

The term micronutrients is used to describe vitamins and minerals in general.

Macronutrients, on the other hand, include proteins, fats and carbohydrates.

Humans must obtain micronutrients from food since our body cannot produce vitamins and minerals for the most part. That's why they're also referred to as essential nutrients.

Vitamins are organic compounds made by plants and animals which can be broken down by heat, acid or air. On the other hand, minerals are inorganic, exist in soil or water and cannot be broken down.

When you eat, you consume the vitamins that plants and animals created or the minerals they absorbed.

The micronutrient content of each food is different, so it's best to eat a variety of foods to get enough vitamins and minerals.

An adequate intake of all micronutrients is necessary for optimal health, as each vitamin and mineral has a specific role in your body.

Vitamins and minerals are vital for growth, immune function, brain development and many other important functions.

Depending on their function, certain micronutrients also play a role in preventing and fighting disease.

Macrominerals

Macrominerals are needed in larger amounts than trace minerals in order to perform their specific roles in our body.

The macrominerals and some of their functions are:

i) **Calcium:** Necessary for proper structure and function of bones and teeth. Assists in muscle function and blood vessel contraction).

ii) **Phosphorus:** Part of bone and cell membrane structure

iii) **Magnesium:** Assists with over 300 enzyme reactions, including regulation of blood pressure).

iv) **Sodium:** Electrolyte that aids fluid balance and maintenance of blood pressure

v) **Chloride:** Often found in combination with sodium. Helps maintain fluid balance and is used to make digestive juices

vi) **Potassium:** Electrolyte that maintains fluid status in cells and helps with nerve transmission and muscle function

v) **Sulfur:** Part of every living tissue and contained in the amino acids methionine and cysteine Sources and recommended intakes of the macrominerals are

Nutrient	Sources	RDA or AI (adults > 19 years)
Calcium	Milk products, leafy greens, broccoli	2,000–2,500 mg
Phosphorus	Salmon, yogurt, turkey	700 mg
Magnesium	Almonds, cashews, black beans	310–420 mg
Sodium	Salt, processed foods, carned soup	2,300 mg
Chloride	Seaweed, salt, celery	1,800–2,300 mg
Potassium	Lentils, acorn squash, bananas	4,700 mg
Sulfur	Garlic, onions, Brussels sprouts, eggs, mineral water	None established

Trace Minerals

Trace minerals are needed in smaller amounts than macrominerals but still enable important functions in our body.

The trace minerals and some of their functions are:

i) **Iron:** Helps provide oxygen to muscles and assists in the creation of certain hormones.

ii) **Manganese:** Assists in carbohydrate, amino acid and cholesterol metabolism.

iii) **Copper:** Required for connective tissue formation, as well as normal brain and nervous system function.

iv) **Zinc:** Necessary for normal growth, immune function and wound healing.

v) **Iodine:** Assists in thyroid regulation.

vi) **Fluoride:** Necessary for the development of bones and teeth.

vii) **Selenium:** Important for thyroid health, reproduction and defense against oxidative damage.

Nutrient	Sources	RDA or AI (adults > 19 years)
Iron	Oysters, white beans, spinach	8–18 mg
Manganese	Pineapple, pecans, peanuts	1.8–2.3 mg
Copper	Liver, crabs, cashews	900 mcg
Zinc	Oysters, crab, chickpeas	8–11 mg
Iodine	Seaweed, cod, yogurt	150 mcg
Fluoride	Fruit juice, water, crab	3–4 mg
Selenium	Brazil nuts, sardines, ham	55 mcg

Nutrients

The human body is considered as a live chemical laboratory in which several biochemical processes take place at any given time. For proper biochemical processes, we need a balanced diet that includes carbohydrates, proteins, fats, minerals and water. These are different classes of nutrients that are necessary for good health.

Carbohydrates provide energy for the body (approximately 4 KCal of energy is produced by the oxidation of 1 gm of glucose). Proteins are essential for building up the structural units of the body, called cells. Enzymes, some hormones, antibodies, transport molecules (such as as hemoglobin) and fibrinogen (for blood clotting) are all protein molecules. Fats serve as 'reservoirs' of food. Fatty cells are specialized ones that store food, mostly in the form of triglycerides. Minerals are nutrient elements such as calcium, phosphorus, magnesium, iron, iodine, etc. They are the constituents of enzymes, co-enzymes, transport molecules, etc. Water is the medium for most of the biochemical reactions in the body, the transport of nutrients and waste products. In addition to carbohydrates, proteins, fats, minerals and water, it has been ascertained that the body requires certain other nutritional factors called vitamins.

11. Describe the significance of Na and K in the biological system.

Ans :

(a) Sodium

Sodium is an important constituent of extracellular fluids. It is the only salt consumed in diet via sodium chloride (NaCl).

Source of Sodium

Common salt (NaCl), foods, milk and vegetables. Functions of Sodium

1. It is a major ion which helps in the maintenance of muscle and nerve excitability.
2. It strongly affects the distribution of body water through osmosis.
3. It plays a vital role in the maintenance of acid- base balance of the body.
4. It is an important constituent of bicarbonate system of the body.

Deficiency Diseases

Deficiency of sodium is quiet uncommon. Decreased concentrations of sodium lead to decrease in the extracellular fluid, plasma volume, cardiac output and finally to cardiac failure. It causes disturbances in acid-base balance and decrease in the excitability of nerves and muscles.

(b) Potassium

Potassium is an important and the main cation of intracellular fluid.

Source of Potassium

Almost all the food stuffs contain potassium. Functions of Potassium

1. It helps in maintaining intracellular osmotic pressure.
2. It is one of the constituents of buffer system of blood (helps in maintaining pH).
3. It helps in carrying carbondioxide via chloride shift.
4. It inhibits the contraction of muscles (including cardiac muscles) and prolongs their relaxation.

Deficiency Diseases

1. Deficiency of potassium leads to fragility of bones.
2. It may also develop sterility.
3. It may effect the normal functioning of cardiac and skeletal muscles.

(c) Calcium

Calcium is the predominant constituent of protoplasm of the cell. An average of 1200 gms of calcium is present in the human body of which almost 99% is present in the bones. It is also found in blood, teeth, muscles, lymph and cerebrospinal fluid.

Sources of Calcium

Milk, milk products, eggs, cheese, fish, fruits, cereals, green leafy vegetables and drinking water.

Functions of Calcium

1. It is essential for the formation, growth and maintenance of bones and teeth.
2. It helps in coagulation or clotting of blood.
3. It is required for contraction of cardiac muscle, skeletal muscle, smooth muscle and regulation of neuromuscular excitation.
4. It acts as a catalyst in various enzymatic reactions involving lipases, ATPases.

5. It is required for the regulation of capillary permeability.

6. It is needed for transforming light impulses into electric impulses in the retina.

Deficiency Diseases

Deficiency of calcium leads to similar manifestations as that of vitamin D. It causes rickets in children and osteomalacia in adults (mainly in pregnant women).

It also delays clotting of blood and may sometimes give rise to tetany (carpopedal spasm of the hands).

Short Question and Answers

1. What are harmones.

Ans :

Hormones are chemical messengers secreted in small quantities (nanograms to milligrams per day) by ductless glands called the endocrine glands of the body. Unlike vitamins, hormones are produced in the human body. The pituitary. parathyroid, thyroid, adrenal, pancreas are some of the endocrine glands present in humans. Hormones perform varied physiological functions: increase or decrease the rate of reaction, control growth, metabolism and reproduction, and many other functions of the body.

Structurally, all hormones are not alike; they have diverse structure just like vitamins. They may be classified according to structure:

i) Amino acid(L-tyrosine) based hormones, e.g., Thyroxin

ii) Polypeptide and protien-based hormones, e.g., Insulin

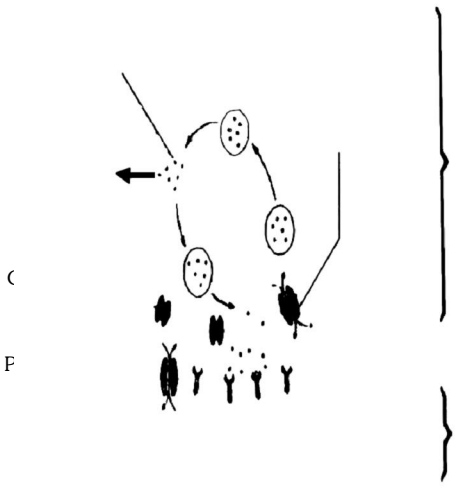
iii) Steroidal hormones, e.g., Testosterone.

2. What are neurotransmitters.

Ans :

Neurotransmitters:

1. Neurotransmitters are endogenous chemicals thai enable neurotransmission It is a type of chemical messenger which transmits signals across a chemical synapse, such as a neuromuscular junction, from one neuron (nerve cell) to another "target" neuron, muscle cell, or gland cell.



2. Electrical signals do not cross the gap between most neurons. They are changed into chemical signals to cross the gap between most neurons so they are changed into chemical signals to cross the gap.

3. Neurotransmitters are released from synaptic vesicles in synapses into the synaptic cleft, where they are received by neurotransmitter receptors on the target cells.

4. Many neurotransmitters are synthesized from simple and plentiful precursors such as amino acids, which arc readily available from the diet and only require a small number of biosynthctic steps for conversion.

5. Neurotransmitters play a major role in shaping everyday life and functions. Their exact numbers are unknown, but more than 200 chemical messengers have been uniquely identified

Importance

Neurotransmitters are the brains chemical that communicate information throughout your brain and body. They relay information between neuron to neuron. Neurotransmitters communicate messages to heart to beat, lungs to breath, and stomach to digest, ft also affects mood, sleep, concentration, etc. Without neurotransmitters your brain would fail to utilize serotonin, dopamine, norepinephrine and much more needed chemicals that is vital to both brain and body.

3. Mention the thyroid harmones.

Ans :

Thyroxine (amino acid based)	Thyroid	Regulates the rate of oxygen consumption and Triiodothyonina (T_3) cellular metabolism (goitre).

4. Write the activity of serotonin.

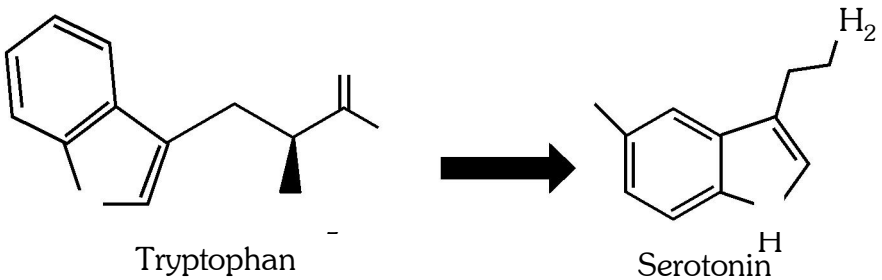
Ans :

Serotonin

1. Serotonin is a chemical nerve cells produce. It sends signals between your nerve cells. Serotonin is found mostly in the digestive system, although it's also in blood platelets and throughout the central nervous system.

2. Serotonin is made from the essential amino acid "tryptophan". This amino acid must enter our body through our diet and is commonly found in foods such as nuts, cheese, and red meat.

3. Tryptophan deficiency can lead to lower serotonin levels. This can result in mood disorders, such as anxiety or depression.



Tryptophan Serotonin

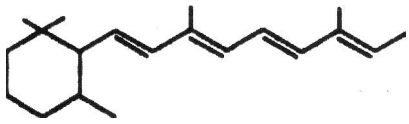
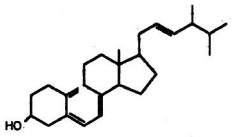
5. Selective serotonin reuptake inhibitor (SSRI)

Ans :

1. A selective serotonin reuptake inhibitor (SSRI) is a type of anti-depressant medication.
2. SSRIs block the reabsorption (reuptake) of serotonin in the brain, making more serotonin available. SSRIs are called selective because they seem to primarily affect serotonin, not other neurotransmitters. SSRIs also may be used to treat conditions other than depression, such as anxiety disorders.
3. E.g., paroxetine (brandname Paxil), fluoxetine (brandname Prozac) sertraline (brandname Zoloft).
4. Fluoxetine is an oral drug that is used primarily for treating depression.
5. Fluoxetine is a racemic mixture of the R and S enantiomers and are equivalent pharmacologic activity.
6. Fluoxetine used to treat major depressive disorder (MDD), moderate to severe bulimia nervosa, obsessive-compulsive disorder (OCD), premenstrual dysphoric disorder (PMDD), panic disorder with or without agoraphobia and in combination with olanzapine for treatment-resistant or bipolar I depression.
7. According to the amines hypothesis, a functional decrease in the activity of amines, such as serotonin and norepinephrine, would result in depression; a functional increase in the activity of these amines would result in mood elevation.

6. Write any two vitamins.

Ans :

A. Fat-soluble Vitamins	
Retinol (Vitamin A) 	- Prevents night blindness by regeneration of rhodopsin (visual purple) and protects *CH_2OH the eye from infection - Deficiency causes light sensitivity, night blindness, xerophthalmia - Fish, liver, eggs, butter, cheese; β- carotene in carrots is a provitamin (vitamin precursor)
Calciferol (Vitamin D_2) 	- Aids in Ca and P metabolism and is essential in building strong bones - Deficiency causes rickets - Cod liver oil, irradiated ergosterol (vitamin D) as a milk supplement

7. Micronutrient.

Ans :

Micronutrients are one of the major groups of nutrients our body needs. They include vitamins and minerals.

Vitamins are necessary for energy production, immune function, blood clotting and other functions. Minerals play an important role in growth, bone health, fluid balance and several other processes.

The term micronutrients is used to describe vitamins and minerals in general.

Macronutrients, on the other hand, include proteins, fats and carbohydrates.

Humans must obtain micronutrients from food since our body cannot produce vitamins and minerals for the most part. That's why they're also referred to as essential nutrients.

Vitamins are organic compounds made by plants and animals which can be broken down by heat, acid or air. On the other hand, minerals are inorganic, exist in soil or water and cannot be broken down.

When you eat, you consume the vitamins that plants and animals created or the minerals they absorbed.

The micronutrient content of each food is different, so it's best to eat a variety of foods to get enough vitamins and minerals.

An adequate intake of all micronutrients is necessary for optimal health, as each vitamin and mineral has a specific role in your body.

Vitamins and minerals are vital for growth, immune function, brain development and many other important functions.

Depending on their function, certain micronutrients also play a role in preventing and fighting disease.

8. Macronutirents

Ans :

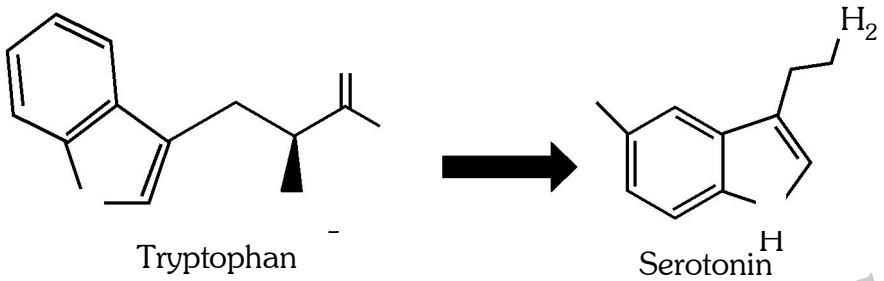
The human body is considered as a live chemical laboratory in which several biochemical processes take place at any given time. For proper biochemical processes, we need a balanced diet that includes carbohydrates, proteins, fats, minerals and water. These are different classes of nutrients that are necessary for good health.

Carbohydrates provide energy for the body (approximately 4 KCal of energy is produced by the oxidation of 1 gm of glucose). Proteins are essential for building up the structural units of the body, called cells. Enzymes, some hormones, antibodies, transport molecules (such as as hemoglobin) and fibrinogen (for blood clotting) are all protein molecules. Fats serve as 'reservoirs' of food. Fatty cells are specialized ones that store food, mostly in the form of triglycerides. Minerals are nutrient elements such as calcium,

phosphorus, magnesium, iron, iodine, etc. They are the constituents of enzymes, co-enzymes, transport molecules, etc. Water is the medium for most of the biochemical reactions in the body, the transport of nutrients and waste products. In addition to carbohydrates, proteins, fats, minerals and water, it has been ascertained that the body requires certain other nutritional factors called vitamins.

9. Draw the structures of serotanin and Dpomin.

Ans :

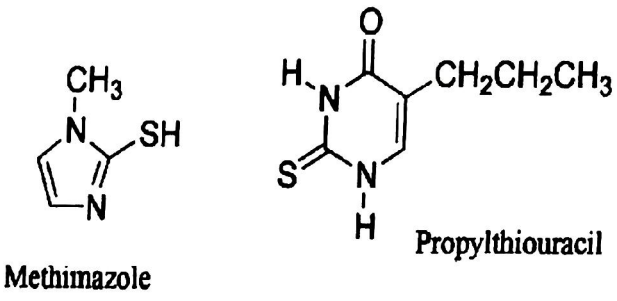


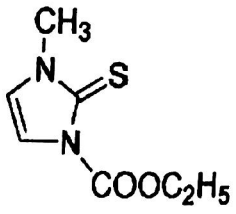
10. Write about Antithyroid drug.

Ans :

Anti thyroid drug:

The ant thyroid drugs include carbimazole, methimazole, propylthiouracil (PTU). These drugs are used to treat hyperthyroidism (overactivity of the thyroid gland). These drugs reduce the excessive thyroid activity and thereby avoids surgery.





11. Write about atenolol

Ans :

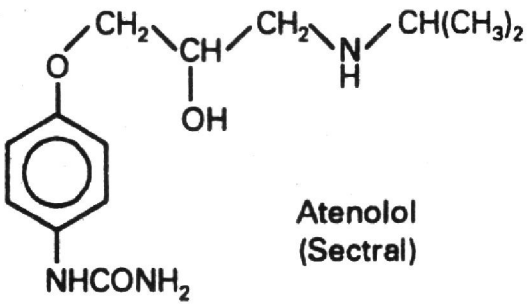
Hypertension is a common disease from which many people suffer. The terms hypertension refer to high blood pressure and hypotension to low blood pressure. Hypertension has been defined, according to the World Health Organisation (WHO), as a measurement of the systolic (contraction of the heart) blood pressure in excess of 140 mm Hg and diastolic (expansion of the heart) blood pressure exceeding 90 mm Hg. The normal adult should have a systolic pressure equal to or below 140 mm Hg together with a diastolic pressure equal to or below 90 mm Hg. Blood pressure is measured with an instrument called a 'sphygmomanometer'.

The exact cause of hypertension is unknown, but we do know that hypertension is the result of defects in the haemodynamic and biochemical functions of the body. The conditions leading to hypertension include obesity, increased salt intake, excessive use of alcohol, cigarette smoking, atherosclerotic complications, and those associated with pregnancy.

The small arterioles used for transporting blood from the arteries to the tissue capillaries, and veins carrying blood to the heart get excessive stimulation due to the sympathetic nervous system. This results in arteriole contraction and increased resistance to the flow of blood. As a result, the blood pressure increases. The other causes for elevated B.P. are tension and emotional stress, which lead to the increased production of octapeptide Angiotensin-ll.

Any medicine used for counteracting this condition of reducing blood pressure and its accompanying symptoms, is known as an antihypertensive or hypotensive drug. An ideal antihypertensive drug should reduce blood pressure through vasodilation, without any side effects or development of tolerance through continuous usage. The drug should be administrable orally. The classification and follow-up of blood pressure measurements according to "The Fifth Report of the Joint National Committee on Detection, Education, and Treatment of High Blood Pressure (JNC-V).

β-blockers; propranolol (inderal), atenolol (sectral);



Atenolol
(Sectral)

Choose the Correct Answers

1. Exampkle of Amino acid based hormone. [a]
   (a) Thyroxin (b) Insulin
   (c) Testosterone (d) All the above
2. The drug used to treat major depressive disorder _____. [a]
   (a) Fluoxetine (b) Seratonin
   (c) Dopamine (d) All the above
3. Fat soluble vitamins are _____. [b]
   (a) B, C (b) A, D, E, K
   (c) Both A and B (d) Nil
4. Example for polypeptide and proteon based hormone _____ [b]
   (a) Thyroxine (b) Insulin
   (c) Testosterone (d) None of the above
5. _____ element is used for proper structure and fucntion of bones and teeth. [c]
   (a) Mg^{+2} (b) $2n^{+2}$
   (c) Ca^{+2} (d) All
6. Anemia is caused due to a deficiency of _____ vitamin. [b]
   (a) Vitamin c (b) Folic acid
   (c) Vitamin (d) Vitamin E
7. Insulin secreted by _____ [c]
   (a) Stomach (b) Kideny
   (c) Pancreas (d) Instestine
8. In terms of R–S configuration L-Dopa corresponds to _____ [b]
   (a) R-Dopa (b) S-Dopa
   (c) Racemic mixture (d) All the above
9. _____ vitamin is often called the sunshine vitamin. [b]
   (a) Vitamin A (b) Vitamin D
   (c) Vitamin C (d) Vitamin E
10. _____ element used for thyroid regulation. [a]
    (a) Iodine (b) Sodium
    (c) Potassium (d) Magnesium

Fill in the Blanks

1. Chemical messengers scretes in small quantitites by ductless glands of the body are known as _____.
2. Chemical messengers transmits signals from are neuron to another neuron, or muscle cell (or) gland cell are _____.
3. _____ secreted by thyroid gland.
4. Other name of salbutamol drug is _____.
5. Deficiency of serotun causes _____.
6. _____ is a precursor of norepinephrine.
7. L-Dopa cures _____ disease.
8. Water soluble vitamins are _____.
9. _____ Element is necessary for normal growth, imune function and wound healing.
10. Example for antithyroid durg _____.

ANSWERS

1. Harmones
2. Neurotransmitters
3. Thyroxin
4. Albutera
5. Mood disorders
6. Dopamine
7. Parkinson
8. B and C vitamins
9. Zinc
10. Carbimazole

FACULTY OF SCIENCE

B.Sc. VI Semester (CBCS) Examination

Subject : Medicinal Chemistry

Paper-VI-A

MODEL PAPER - I

Time : 3 Hours] [Max. Marks : 80

Part - A (8 × 4 = 32 Marks)

Note : Answer any Eight questions

ANSWERS

1. What is pharmacophore give example. **(Unit-I, SQA - 5)**
2. What is Diseases ? **(Unit-I, SQA - 1)**
3. What is ADMET? **(Unit-I, SQA - 7)**
4. What are enzymes? **(Unit-II, SQA - 1)**
5. Define Antagonists. **(Unit-II, SQA - 4)**
6. Write any three factos effecting enzyme action. **(Unit-II, SQA - 8)**
7. Draw the structure of dapsone and its preparation and therapeutic activity. **(Unit-III, SQA - 1)**
8. Write the synthesis and therapeutic activity of AZT. **(Unit-III, SQA - 5)**
9. Give the cardiovascular drugs with examples. **(Unit-III, SQA - 9)**
10. Write about Antithyroid drug. **(Unit-IV, SQA - 10)**
11. Write about any two vitamins. **(Unit-IV, SQA - 6)**
12. Write the activity of serotonin. **(Unit-IV, SQA - 4)**

Part - B (4 × 12 = 48 Marks)

Note : Answer all the questions

13. (a) Give the chemical, Generic names & Trade names with examples. **(Unit-I, Q.No. 11)**

OR

(b) Give metabolites & antimetabolites. **(Unit-I, Q.No. 9)**

14. (a) Classify the enzyme inhibitors and write the examples. **(Unit-II, Q.No. 5)**

OR

(b) Discuss the binding role of $-NH_2$ group Quaternary ammonium salts and double bond drug binding receptor interactions. **(Unit-II, Q.No. 11)**

15. (a) Mention the synthesis of Isoniazid and its therapeutic activity. **(Unit-III, Q.No. 5)**

OR

(b) Write the synthesis and therapeutic activity of chloroquine. **(Unit-III, Q.No. 4)**

16. (a) Write the synthesis of antithyroid drug carbimazol. **(Unit-IV, Q.No. 4)**

OR

(b) Mention the adrenergic drugs synthesis and Therapeutic activity. **(Unit-IV, Q.No. 5)**
Discuss the synthesis of atenelol and salbutamol.

FACULTY OF SCIENCE

B.Sc. VI Semester (CBCS) Examination

Subject : Medicinal Chemistry

Paper-VI-A

MODEL PAPER - II

Time : 3 Hours] [Max. Marks : 80

Part - A (8 × 4 = 32 Marks)

Note : Answer any Eight questions

ANSWERS

1. Define distribution and write the effect of plasma protein inbinding. **(Unit-I, SQA - 8)**
2. Give the standard name of API and define it. **(Unit-I, SQA - 3)**
3. What is therapeutic index. **(Unit-I, SQA - 6)**
4. Write about covalent bonding interactions in drug receptor complex. **(Unit-II, SQA - 6)**
5. Write about Irreversible enzyme inhibitors. **(Unit-II, SQA - 3)**
6. Write about reversible competitive inhibition. **(Unit-II, SQA - 9)**
7. Draw the Pencillins structures. **(Unit-III, SQA - 2)**
8. Define Anesthetics. **(Unit-III, SQA - 4)**
9. Discuss the Benzocaine local anaesthetic. **(Unit-III, SQA - 6)**
10. Write the activity of serotonin. **(Unit-IV, SQA - 4)**
11. What are neurotransmitters. **(Unit-IV, SQA - 2)**
12. Selective serotonin reuptake inhibitor (SSRI) **(Unit-IV, SQA - 5)**

Part - B (4 × 12 = 48 Marks)

Note : Answer all the questions

13. (a) What are receptors give examples? **(Unit-I, Q.No. 8)**

OR

(b) Explain pharmacodynamics & pharmacokinetics. **(Unit-I, Q.No. 7)**

14. (a) Explain the Drug action - receptor theory. **(Unit-II, Q.No. 7)**

OR

(b) Mention the drug receptor interactions involved in drug receptor complex. **(Unit-II, Q.No. 10)**

15. (a) Explain the semisynthesis of pencillin–G. **(Unit-III, Q.No. 3)**

OR

(b) Mention the drug to treat diabetis mellitus and give the therapeutic activity. **(Unit-III, Q.No. 8)**

16. (a) Discuss the synthesis of anti-parkinson drug levodopa. **(Unit-IV, Q.No. 8)**

OR

(b) Write about Micro and Macro nutrients. **(Unit-IV, Q.No. 10)**

FACULTY OF SCIENCE

B.Sc. VI Semester (CBCS) Examination

Subject : Medicinal Chemistry

Paper-VI-A

MODEL PAPER - III

Time : 3 Hours] [Max. Marks : 80

Part - A (8 × 4 = 32 Marks)

Note : Answer any Eight questions

ANSWERS

1. Write about pharmaceuticals. **(Unit-I, SQA - 4)**
2. Metabolites **(Unit-I, SQA - 10)**
3. Define drug. **(Unit-I, SQA - 2)**
4. Describe the structure activity relationships of sulfonomides. **(Unit-II, SQA - 10)**
5. Write about Irreversible enzyme inhibitors. **(Unit-II, SQA - 2)**
6. Define agonists and mention the types of agonists. **(Unit-II, SQA - 5)**
7. Explain the synthesis of Antic cancer cisplatin and its therapeutic activity. **(Unit-III, SQA - 3)**
8. Write the Synthesis of Paracetamol. **(Unit-III, SQA - 8)**
9. Synthesis of Nitrous oxide. **(Unit-III, SQA - 7)**
10. Mention the thyroid harmones. **(Unit-IV, SQA - 3)**
11. Write a short note Macronutirents **(Unit-IV, SQA - 8)**
12. Write a short nore on Micronutrient **(Unit-IV, SQA - 7)**

Part - B (4 × 12 = 48 Marks)

Note : Answer all the questions

13. (a) Classify the drugs based on structures & therapeutic activity with examples. **(Unit-I, Q.No. 12)**

OR

(b) Explain metabolism in phase I & phase II reactions. **(Unit-I, Q.No. 16)**

14. (a) Write the factors affecting enzyme action. **(Unit-II, Q.No. 2)**

OR

(b) Discuss the enzyme inhibitors and their importance. **(Unit-II, Q.No. 4)**

15. (a) Explain the semisynthesis of pencillin–G. **(Unit-III, Q.No. 3)**

OR

(b) Give the cardiovascular drugs with examples. **(Unit-III, Q.No. 9)**

16. (a) What are neurotransmitters. **(Unit-IV, Q.No. 2)**

OR

(b) Explain the SSRIS of fluoxetine and dopamine. **(Unit-IV, Q.No. 7)**

FACULTY OF SCIENCE

B.Sc. VI Semester (CBCS) Examination

Subject : Medicinal Chemistry

Paper-VI-A

MAY/JUNE - 2019

Time : 3 Hours] [Max. Marks : 60

Part - A (5 × 3 = 15 Marks)

Note : Answer any five of following questions

1. Define Pharmacology, Pharmacodynamics and Pharmacophore.
2. Give the generic name and trade name for any two drugs.
3. Explain briefly the role of OH group and double bond in drug receptor complex formation.
4. What are agonists and antagonists? Give examples.
5. What are anti-diabetic and antipyretic drugs? Give one example for each.
6. Write the synthesis and therapeutic activity of Dapson.
7. What are hormones ? Give two examples.
8. What are micronutrients? How Na and Ca are helpful for good health.

Part - B (45 Marks)

Note : Answer all the questions

9. (a) (i) Give the classification of drugs based on therapeutic activity with examples.
   (ii) Discuss about routes of administration of drugs.

   OR

   (b) (i) Describe briefly Phase I and Phase II reactions in metabolism of drugs.
   (ii) Write a short note on metabolites and antimetabolites.

10. (a) (i) Write the mechanism of enzyme catalyzed reactions.
   (ii) Discuss about different types of enzyme inhibition.

   OR

   (b) (i) Explain the factors affecting the enzymatic reactions.
   (ii) Explain the structure activity relationship studies of Sulfonamides.

11. (a) Write the synthesis and therapeutic activity of Omeprazole, Benzocaine and Cisplatin.

   OR

   (b) (i) Discuss about general and local anesthetics.
   (ii) Write the semi synthesis and therapeutic activity of Penicillin-G.

12. (a) (i) What are adrenergic drugs? Write the structure and therapeutic activity of Salbutamol.
   (ii) Discuss about the sources and deficiency disorder of water soluble vitamins.

   OR

   (b) (i) Write about the deficiency disorders of A, D, E vitamins.
   (ii) Discuss about the drug action of Dopamine and Levodopa.

FACULTY OF SCIENCE

B.Sc. VI Semester (CBCS) Examination

Subject : Medicinal Chemistry

Paper-VI-A

September / October - 2020

Time : 2 Hours] [Max. Marks : 60

Part - A (3 × 5 = 15 Marks)

Note : Answer any three of following questions

1. Distinguish the term generic name from trade name with an example.
2. Define the following
   (a) Metabolites
   (b) Pharmacokinetics
   (c) Pharmacology
3. What are inhibitors? Explain with an example.
4. Name any two drugs which are used in the treatment of metabolic disorders.
5. Give an example for antipyretic, antacid and anti inflammatory drugs.
6. What are health promoting drugs? Write any two examples.
7. What are Hormones? Give an example.
8. Write the synthesis of sulphanilamide.

Part - B (3 × 15 = 45 Marks)

Note : Answer any three questions

9. Define the term drag and explain the characteristics of drags.
10. Write a note on "drags acting on renal elimination".
11. What are inhibitors? Explain the different types of enzyme inhibitors.
12. Define the terms Receptor and explain "drug action - receptor theory".
13. Write a note on drugs acting on nervous system with an example.
14. Write the synthetic and therapeutic activity of Chloroquine.
15. What are micronutrients? Explain the sources of vitamin A and D.
16. Explain about drug action on Levodopa and Dopamine diseases.

FACULTY OF SCIENCE

B.Sc. VI Semester (CBCS) Examination

Subject : Medicinal Chemistry

Paper-VI-A

November / December - 2021

Time : 2 Hours] [Max. Marks : 60

Part - A (3 × 5 = 15 Marks)

Note : Answer any three of following questions

1. Define the following,
   (a) Pharmacokinetics
   (b) Pharmacology
2. How chemical names are different from trade names?
3. Explain the following,
   (a) Enzyme
   (b) Receptor.
4. Write a note on structure - activity relationship of drug molecule with an example.
5. Give any two drugs which act on nervous system.
6. Define the term 'Chemotherapeutic agents'.
7. What are health promoting drugs?
8. Write a note on deficiency disorder of vitamin 'A'.

Part - B (3 × 15 = 45 Marks)

Note : Answer any three questions

9. Give the classification of drugs based on structures and therapeutic activity with examples
10. Write a note on 'absorption of drugs across the membrane".
11. Explain the binding role of-NH_2 group in drug receptor interaction.
12. Explain the factors affecting on enzyme action.
13. Define the term drug. Explain the drugs to treat of the following. Antidiabetic, Antacid, Anti-inflammatory drugs.
14. Write the synthesis and therapeutic activity of
    (a) Sulphanilamide
    (b) Chloroquine.
15. Define the term "hormone" and explain the role of hormones
16. Explain the deficiency disorders and remedy of Vitamin B, D and K.

FACULTY OF SCIENCE

B.Sc. VI Semester (CBCS) Examination

Subject : Medicinal Chemistry

Paper-VI-A

June / July - 2022

Time : 3 Hours] [Max. Marks : 80

Part - A (8 × 4 = 32 Marks)

Note : Answer any EIGHT questions

ANSWERS

1. Define Pharmacology and Pharmacophore. **(Unit-I, Q.No. 6)**

Ans :

It is the science of identification of drugs or the study of the effects of biologically active substances on the human or animal system.

2. What are the generic names and trade name of drugs? Give examples. **(Unit-I, Q.No. 11)**
3. What is API? Explain. **(Unit-I, Q.No. 4)**
4. Discuss the binding role of quaternary ammonium salts. **(Unit-II, SQA. 7)**
5. What is reversible and irreversible inhibition of enzymes? Give examples. **(Unit-II, SQA. 3, 9)**
6. What are drug receptors?

Ans :

Paul Ehrlich was the first scientist to coin the term receptor in 1907. According to Ehrlich, compounds are not able to exert their effect unless they are bound. Receptors play an important role in enabling communication between the cells, as they help in coordinating the functioning of all the body cells. Most of the receptors are actually proteins which are found on the cell membrane and possess a binding site on the extracellular site. This binding site, itself, has no activity but helps in the binding of drugs or chemical messengers which can be hormones or neurotransmitters. These hormones are secreted by specific glands and these bind to only specific receptors. Neurotransmitters are chemicals which are released from the nerve terminals on receiving appropriate signals.

7. What is therapeutic activity? **(Unit-III, Q.No. 1)**
8. Discuss the synthesis of sulphanilamide. **(Unit-III, Q.No. 1)**
9. Write about anti-inflamantory drugs.

Ans :

The drugs which relieve inflammatory conditions are referred as anti-inflammatory drugs.

10. What are vitamins? **(Unit-IV, Q.No. 9)**
11. Write about hormones. **(Unit-IV, SQA. 1)**
12. Discuss about dopamine. **(Unit-IV, Q.No. 7)**

Part - B (4 × 12 = 48 Marks)

Note : Answer all the questions

13. (a) (i) Give the classification of drugs based on structures. Give suitable examples. **(Unit-I, Q.No. 12)**

(ii) Write about metabolites and anti-metabolites. **(Unit-I, Q.No. 9)**

OR

(b) Explain the following:

(i) Toxicity **(Unit-I, Q.No. 18)**

(ii) Phase I and Phase II reactions. **(Unit-I, Q.No. 16)**

14. (a) (i) Describe the mechanism of enzyme action. **(Unit-II, Q.No. 2)**

(ii) Explain structure-activity relationship of drug molecules. **(Unit-II, Q.No. 12)**

OR

(b) (i) Explain the concepts of agonists and antagonists with examples. **(Unit-II, Q.No. 8, 9)**

(ii) Discuss the mechanism of drug action.

Ans :

1. Positions of the sulfonyl and amino groups have an important role in antibacterial activity of sulfonamides. Optimum activity is observed in 1,4-arrangement of the amino and sulfonyl groups, provided that there is no substituent on amino group.
2. The activity of sulphonamides is mainly due to the amino (N^4) group, hence its modification produces inactive compounds.
3. The presence of $S0_2$ moiety imparts electropositive character to the adjacent nitrogen atom which in turn makes the functional group acidic in nature (by imparting acidity to the hydrogen atoms adjacent to nitrogen).
4. Monosubstitution at N^1 usually enhances the activity whereas disubstitution at N^1 nullifies the activity.
5. When one of the hydrogen atoms of NH, is displaced by an electron withdrawing (electron loving) heteroatomic ring, the remaining hydrogen atom becomes highly acidic. This results in an increase in the antibacterial activity, as well as enhanced stability of the salt so formed.
6. Removal of benzene ring from the compound and introduction of other ring systems decreases the activity. Moreover, addition of more substituents on benzene ring shows derailment of activity.

15. (a) Explain the synthesis and therapeutic activity of Chloroquin and Cisplatin. **(Unit-III, Q.No. 4, 6)**

OR

(b) (i) Describe the activity of drugs in the treatment of diabetics with an example. **(Unit-III, Q.No. 8)**

(ii) Define and classify the anesthetics with suitable examples.

Ans :

Local anaesthetics are the chemical agents which reversibly block the action potential on any part of the neuron when applied locally in appropriate concentrations. These cause temporary loss of autonomic control, sensory and motor impulses and result in muscular paralysis without affecting the consciousness.

General anaesthetics are the drugs which are given systemically during surgical procedures. These are a class of CNS depressant drugs which produce partial or total loss of sensation of pain with a controlled and reversible depression of the functional activity of the CNS (cerebral cortex, basal ganglia, cerebellum and spinal cord). They act on the CNS and cause analgesia, amnesia (reversible loss of memory), loss of consciousness with the relaxation of all body muscles and blockade of autonomic and sensory reflexes, thus aids in performing complicated surgical procedures.

16. (a) (i) Discuss the significance of Adrenergic drugs with examples. **(Unit-IV, Q.No. 5)**

(ii) What are micronutrients? Describe the significance of Na and K in the biological system. **(Unit-IV, Q.No. 10, 11)**

OR

(b) (i) Explain the significance and action of serotonin and fluoxetine.

Ans :

Serotonin 5-hydroxytryptamine or 5-HT is or a potential inhibitory neurotransmitter which modulates homeostasis and nociception (sensory pathways). It also mediates brain functions and plays an important role in temperature regulation, eating disorders and affective disorders (schizophrenia and depression).

(ii) Describe the sources, deficiency disorders and remedy of vitamin C and E. **(Unit-IV, Q.No. 9)**